Anesthesia AND Analgesia

.....CURRENT RESEARCHES

Some Gas Machine Hazards and Their Elimination ..... Page 26

Hemodynamic Effects of Morphine During and Early After Cardiac Operations ..... Page 47

Final Program for 1976 Congress ..... Page 151

Table of Contents ..... Page (4)

Oldest Publication in the Specialty - Established 1922

Journal of the International Anesthesia Research Society

Volume 55, No. 1 January-February, 1976

50th Congress

Las Vegas, Nevada - March 14-18, 1976

Introducing the NEW Mark 14 Wright respirometer

Harlake

Latest in the range of BOC Wright respirometers, this new Mark 14 has been designed to simplify procedures for measuring inspired or exhaled tidal and minute volumes in adults and children.

The re-designed movement and face presentation provides clear, precise indications of volume up to 10 litres. The large hand states volumes between 0-1 litre, graduated in .05 litre increments. The smaller hand states volumes between 0-10 litres and is graduated in 1 litre increments.

The new case incorporates inlet and outlet connections compatible with the proposed ISO standard 22 mm. connections. A new set of circuit adaptors permits complete male/female sequencing as well as connection to 15 mm. ISO tracheal tube connections.

The instrument responds to gas flow in one direction only indicated by an arrow. With this guidance, it is a simple matter to place the respirometer in circuit on either the inspiratory or expiratory side of the patient. Circuit adaptors may be used if necessary to ensure correct sequencing of connections. When placed in-circuit with a mechanical ventilator, the respirometer is normally unaffected by pressure changes.

For specifications on the new Mark 14 and other Wright respirometer models, contact your authorized Harris-Lake dealer or write to Harris-Lake, Inc.

HARRIS-LAKE, INC. A Medishield Company

new flexible Fiber Optic Laryngoscope

direct vision for difficult intubations

The first flexible fiberscope specifically for endotracheal intubations.

Portable, and with its own integral lighting system, the Flexible Fiber Optic Laryngoscope is inserted into the trachea under direct vision.

The articulating end-tip enables it to be directed into position for passage through the vocal cords. The scope then acts as a guide over which the endotracheal tube is passed.

When intubation is achieved, the scope is withdrawn leaving the tube in place.

The complete Flexible Fiber Optic Laryngoscope includes a 49 cm. flexible length, battery handle, 2 C cells, adjustable illumination, spare lamp and a special, foam-lined carrying case.

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
WE STRIVE ALWAYS FOR WORLD CONQUEST OF PAIN
1922

Anesthesia AND Analgesia . . . Current Researches

SCIENTIFIC ARTICLES—January-February, 1976 (Continued)

ABSENCE OF AUTOREGULATION OF CEREBRAL BLOOD FLOW DURING HALOTHANE AND ENFLURANE ANESTHESIA—Miletich, Ivankovich, Albrecht, Reimann, Rosenberg and McKissic 100

SUCCESSFUL USE OF A REDUCED DOSE OF PROTAMINE AFTER CARDIOPULMONARY BYPASS—Guffin, Dunbar, Kaplan and Bland 110

EFFECT OF MECHANICAL VENTILATION WITH END-INSPIRATORY PAUSE ON BLOOD-GAS EXCHANGE—Fuleihan, Wilson and Pontoppidan 122

HEMODYNAMIC EFFECTS OF ISOFLURANE AND HALOTHANE IN PATIENTS WITH CORONARY ARTERY DISEASE—Mallow, White, Cucchiara and Tarhan 135

THOUGHTS ABOUT MEDICAL WRITING. XXXIII. PARALLELISM IS A VIRTUE—Roland .. 139

CASE HISTORY NUMBER 88: GAS EMBOLISM DURING ENCEPHALOGRAPHY—Paul and Munson 141

BRIEF REPORTS

FIRE HAZARD DURING CO_2 LASER MICROSURGERY ON THE LARYNX AND TRACHEA—Snow, Norton, Saluja and Estanislao 146

A NEW INTRODUCER FOR PERCUTANEOUS CARDIOVASCULAR CATHETERS—Gooding and Corssen 148

PLASTIC COVERED SOLID COPPER WIRE STYLET—Nicholson 150

FEATURES

People and Places ..... (25)
Editor's Choice 22
The Physician and The Law 45
CORRECTION: Comparison of Methotrimeprazine and Meperidine as Components of Balanced Anesthesia — Radnay, Becsey, Shah and Foldes 46
We Salute—Evan Lloyd Frederickson, M.D. .. 67
Medical Statistics 82
Correspondence 114
Questions and Answers 131
Program, 50th Annual Congress 151
Book Shelf 164
Scientific Articles, Next Issue ..... (41)
A Guide for Authors ..... (42)
Back Issues Available ..... (44)
Something New ..... (56)
Classified Advertising ..... (62)
Index of Advertisers ..... (69)

CU6-H0408-1-P024572

Anesthesia AND Analgesia ...CURRENT RESEARCHES

JOURNAL OF THE INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

3645 Warrensville Center Road • Cleveland, Ohio, U.S.A. 44122 • Telephones: (216) 295-1124, 295-1130

P24572

EDITORIAL BOARD

Editor: T. H. Seldon, M.D., Rochester, Minnesota

Associate Editors: John T. Martin, M.D., Toledo, Ohio
Emerson A. Moffitt, M.D., Halifax, Nova Scotia
Edwin S. Munson, M.D., Gainesville, Florida
Robert K. Stoelting, M.D., Indianapolis, Indiana

Contributing Editors: Douglas B. Craig, M.D., Winnipeg, Manitoba
E. Paul Didier, M.D., Rochester, Minnesota
Ronald W. Dunbar, M.D., Atlanta, Georgia
David E. Longnecker, M.D., Charlottesville, Virginia
Dean H. Morrow, M.D., Houston, Texas

ANESTHESIA AND ANALGESIA . . . Current Researches is published bimonthly by the International Anesthesia Research Society, a non-profit scientific and educational corporation of the state of Ohio. Members of the Board of Trustees of the Society are: Paul R. Dumke, M.D., Kenneth K. Keown, M.D., John T. Martin, M.D., Emerson A. Moffitt, M.D., Edwin S. Munson, M.D., B. B. Sankey, M.D., T. H. Seldon, M.D., Robert K. Stoelting, M.D., Morris J. Nicholson, M.D., Emeritus Trustee.

EDITORIAL CORRESPONDENCE and manuscripts should be addressed to: **T. H. Seldon, M.D., Editor, Kahler East—Suite C, Rochester, Minnesota 55901, U.S.A. Telephone: (507) 288-8655.** (See "A Guide for Authors" for information concerning manuscript preparation.) Original articles accepted for publication, or papers presented at the Society's annual scientific meetings which are subsequently published in this Journal become the property of the International Anesthesia Research Society, publisher. Reproduction in whole or in part is not permitted except by written consent of the publisher and the author.

BUSINESS CORRESPONDENCE, including subscription and membership payments, single issue purchases, change of address notices, requests for membership applications, should be sent to: **B. B. Sankey, M.D., Executive Secretary and Business Manager, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122. Telephones: (216) 295-1124, 295-1130.**

SUBSCRIPTION RATE: $25.00 per year (6 issues), including postage.

MEMBERSHIP DUES: $25.00 per year, includes a subscription to the Journal. **Membership** available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine or other disciplines who are engaged either in active clinical practice of or research in anesthesiology. **Associate Membership** available to individuals certified, licensed or accredited in anesthesia-related professions (CRNA, ARIT, Physician Assistant). **Educational Membership** (two years for $25.00) available to interns, residents, students in nurse anesthesia and related training programs.

SINGLE ISSUES: $4.50 each for years beginning 1970; $3.00 for years 1954-1969; $2.00 for years 1928-1953. (See "Back Issues Available" or write to Cleveland business office for listing.)

REPRINTS: For single copies, write directly to senior author at address listed on title page. Quantity orders (minimum 100) processed through Cleveland business office, prices on request.

MAILING DATES: Journals mailed 25th of January, March, May, July, September and November. Second Class postage paid at Cleveland, Ohio.

CHANGE OF ADDRESS NOTICES: Send to Cleveland business office by first day of the above months to ensure correct addressing of Journals. Replacement copies of missing Journals will be furnished without charge only if original copy is returned by post office as undeliverable.

ADVERTISING: Rate sheets, including advertising clearance procedure, available from national advertising representative: Charles B. Slack, Inc., 6900 Grove Road, Thorofare, New Jersey 08086—Telephone: (609) 848-1000. Orders, contracts, reproduction materials, set copy and classified ad copy should be sent only to Cleveland office.

©1976, International Anesthesia Research Society

Contents

Volume 55 January-February, 1976 Number 1

SCIENTIFIC ARTICLES

PROPRANOLOL AND SURGICAL ANESTHESIA—Kaplan and Dunbar 1

VISUAL COMMUNICATION: CLARITY IN LECTURE SLIDES REVISITED—McComb 6

ANESTHESIA FOR TRANSCERVICAL THYMECTOMY IN MYASTHENIA GRAVIS—Girnar and Weinreich 13

CHANGES IN AIRWAY RESISTANCE FOLLOWING DROPERIDOL, HYDROXYZINE, AND DIAZEPAM IN NORMAL VOLUNTEERS—Cottrell, Wolfson and Siker 18

SOME GAS MACHINE HAZARDS AND THEIR ELIMINATION—Rendell-Baker 26

CARDIAC FAILURE ASSOCIATED WITH HYPOCALCEMIA—Denlinger and Nahrwold 34

EFFECT OF POSITION (SEMIRECUMBENT VERSUS SUPINE) ON POSTOPERATIVE OXYGENATION IN MARKEDLY OBESE SUBJECTS—Vaughan, Bauer and Wise 37

HYPNOSIS FOR MONITORING INTRAOPERATIVE SPINAL CORD FUNCTION—Crawford, Jones, Perisho and Herring 42

HEMODYNAMIC EFFECTS OF MORPHINE DURING AND EARLY AFTER CARDIAC OPERATIONS—Moffitt, Tarhan, Rodriguez, Barnhorst and Pluth 47

THE PULMONARY ABSORPTION-EXCRETION VOLUME EFFECT—Rackow and Salanitre 51

LARYNGEAL STENOSIS IN ACROMEGALY: A POSSIBLE CAUSE OF AIRWAY DIFFICULTIES ASSOCIATED WITH ANESTHESIA—Hassan, Matz, Lawrence and Collins 57

CAUDAL ANALGESIA FOR QUADRUPLET DELIVERY—Abouleish 61

A REGIONAL ANESTHETIC APPROACH FOR RENAL TRANSPLANTATION—Linke and Merin 69

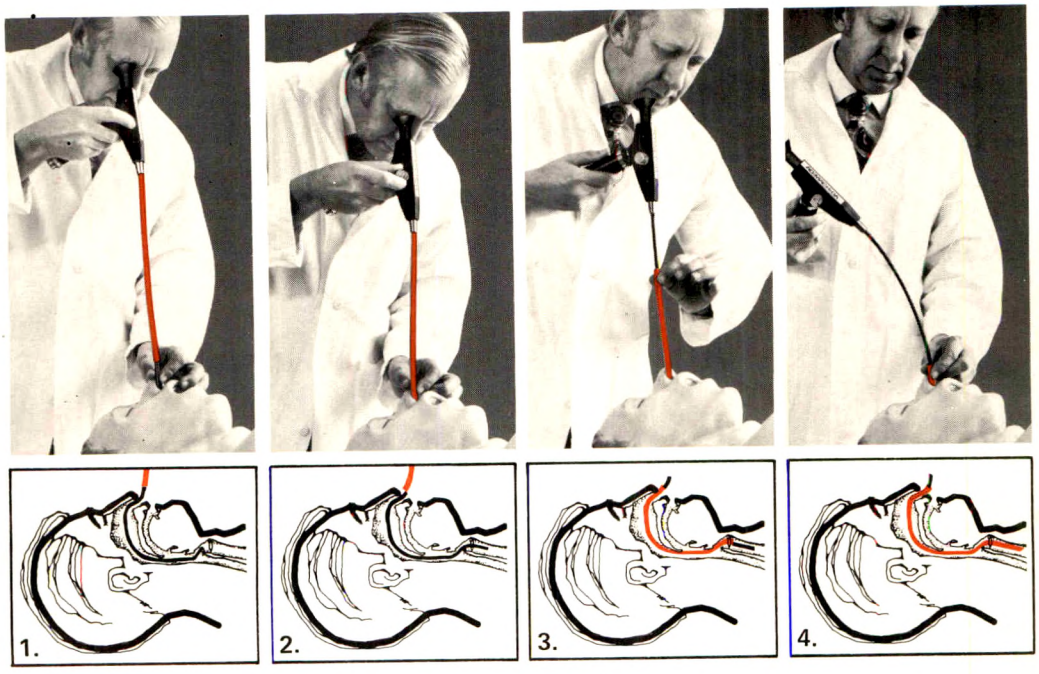
RAPID ANESTHESIA INDUCTION IN COMBAT CASUALTIES WITH FULL STOMACHS—Cromartie 74

CIRCULATORY CHANGES DURING ANESTHETIC INDUCTION: IMPACT OF d-TUBOCURARINE PRETREATMENT, THIAMYLAL, SUCCINYLCHOLINE, LARYNGOSCOPY, AND TRACHEAL LIDOCAINE—Stoelting and Peterson 77

CARDIOVASCULAR EFFECTS OF ENFLURANE AND HALOTHANE ON THE RHESUS MONKEY—Ritzman, Erickson and Miller 85

LOW-DOSE INTRAMUSCULAR KETAMINE FOR PEDIATRIC RADIOTHERAPY: A CASE REPORT—Amberg and Gordon 92

N_2O VOLUMES ABSORBED AND EXCRETED DURING N_2O ANESTHESIA IN CHILDREN—Salanitre and Rackow 95



integral lighting, plus fiber optics forever eliminate "blind" intubations

1. Pass the flexible length through an endotracheal tube. The right hand controls end-tip deflection. The left hand introduces the scope through the nose, and advances it along the posterior wall of the pharynx and beyond the epiglottis.

Deflect the end-tip to see the larynx . . .

2. and pass it through the cords, into the trachea to a depth of about 5 cm.

The scope provides a clear, direct view of the internal anatomy as it travels along the respiratory tract.

3. When the end-tip is well in place within the trachea, simply advance the endotracheal tube. The scope acts as a stylet for the tube, making proper intubation a virtual certainty.

4. Remove the scope when intubation is completed.

Please rush ☐ product literature, ☐ research article reprints.

☐ I am interested also in a demonstration of the AO Flexible Fiberoptic Laryngoscope.

Name _____

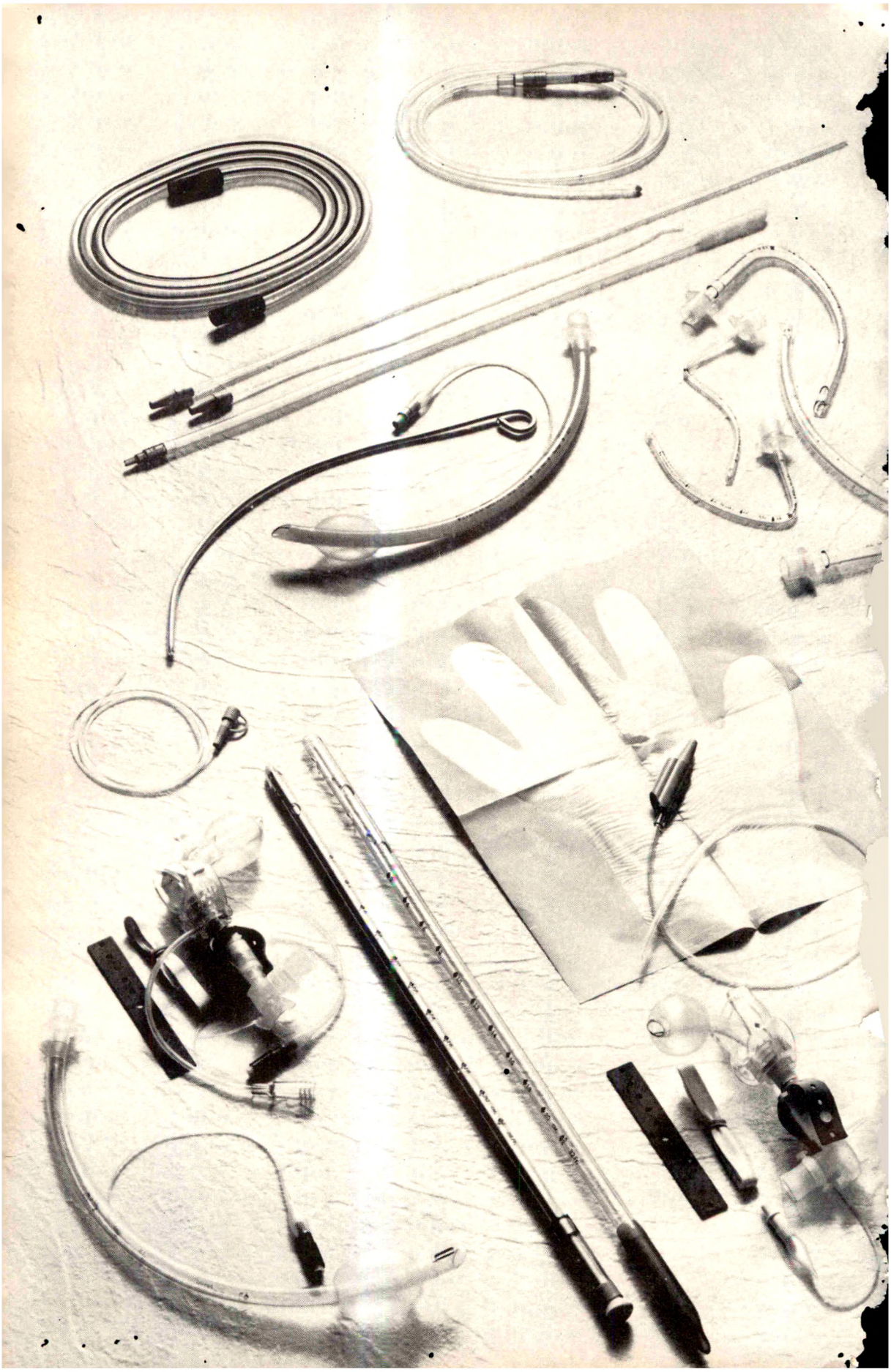
Title _____

Representing _____

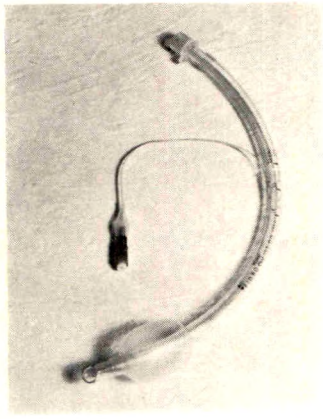
Street _____

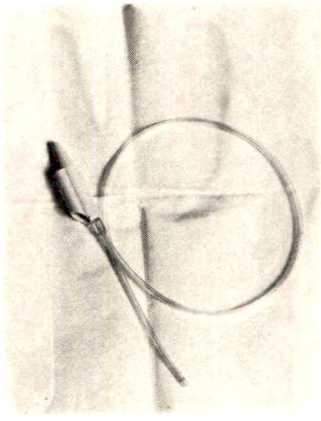
City, State, Zip _____

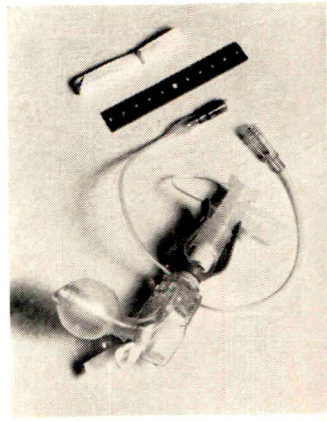
AO® American Optical
MEDICAL DIVISION
Crosby Drive,
Bedford, MA 01730
617 275-0500



National Catheter... we make lifelines.







hi-lo® tracheal tubes*

A high volume, low pressure cuffed endotracheal tube that inflates with a minimum of air pressure. Creates a no-leak seal, usually of less than 25 cm. H_2O; avoids trauma to the tracheal wall.

Soft and pliant tubes have a true murphy tip, intubate easily. Water clear, the tube fogs on exhalation, an instant monitor of patient respiratory function. May be used orally or nasally.

Other trademarks of NCC: **holdtite™, vari-form®, ventrol®, suture rib™, versi-cath®, maxi-flex & vac™, RAE™.**

*Covered under one or more of the following patents, U.S. Pat. No's 3,625,793, 3,605,750, 3,508,554, 3,610,242, and patents pending.

†University of Pittsburgh

Ncc satin-cath™* & gluv set

This sterile, disposable gluv set has met with overwhelming acceptance.

The GENTLE-FLO® catheter has a SATIN-SLIP SURFACE™ that provides smooth, non-binding insertion into an endotracheal tube.

The paperbacked glove slips on easily, fits either hand and is easily removed when suctioning is complete. The set also contains a waterproof receptacle. Pull the marked tabs and it opens and locks in position, ready to use for the receipt of sterile water. Equipped with VACTROL® connector, catheter suction may be simply regulated from full on to off.

Available with catheters in all popular sizes. Packaged in a sterile peel-back paper pouch—50 sets/box.

pitt*† trach speaking tube

This speaking tube permits tracheostomy patients to converse. The emotional benefits are obvious.

The hi-lo® cuff inflates easily to avoid tracheal damage. This possibility is further removed because the clear tubing permits convenient bronchoscopic observation of the tracheal wall. The auxiliary air supply tube is to be connected to a humidified air oxygen outlet to achieve a speaking air flow.

Equipped with Eross Safety Straps and removable spacers and adjustable collar, the trach tube is adaptable to fit any adult patient. The suction port, which may be locked, allows for suctioning of the patient without removing the respirator and introducing a flexible fiberoptic bronchoscope, thus avoiding delays during this critical period.

Manufactured with the precision medicine must demand.

national catheter corp.

A Mallinckrodt® COMPANY

Home of the Sheridan Line of Catheters argyle, new york 12809

In 16 years of use in the United States, FLUOTHANE (halothane) has been administered over 100 million times in a wide variety of surgical procedures. 100 million ...extensive usage and evaluation that attests to FLUOTHANE as the most widely used inhalant anesthetic.

Since it was first introduced, over 4,000 papers worldwide have been published, ranging from review articles to in-depth studies. 4,000 papers... a bibliographic record of note on the most widely used inhalant anesthetic.

In a continuing program of inform tional services on anesthesiology, Ay provides printed and audiovisual aic reflecting the opinions and experie recognized authorities in the field include the highly regarded seri *Anesthesia Rounds* and *Clinica Anesthesiology*, as well as sev educational value—all availa your Ayerst Representative.

FLUOTHANE® (HALOTH ...OVER 100 MILLI ADMINISTRATION

- nonflammable, nonexplosiv
- permits use of high concen oxygen
- allows free use of cautery for adequate control of bleeding
- minimal odor facilitates smooth, rapid induction, reduces patient distress
- early obtundation of pharyngeal and laryngeal reflexes facilitates intubation
- lessens airway problems
- permits rapid adjustment of depth of anesthesia
- emergence is rapid and tranquil with quick recovery of protective reflexes
- minimal nausea and vomiting, shorter recovery room stay

Ayerst

See last page of advertisement for prescribing information.

FLUOTHANE®

brand of halothane

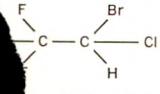
the most widely used inhalant anesthetic

from **Ayerst**

or precision, experience, quality, and service

lete text of package circular.)

tion. FLUOTHANE, brand of halo- an inhalation anesthetic. It is 2-chloro-1, 1, 1-trifluoroethane following structural formula:



gravity is 1.872-1.877 at boiling point (range) is 760 mm. Hg. The vapor mm. Hg at 20° C. The cient is 2.5 at 37° C., and er coefficient is 220 at centrations within anes- nonirritating and have a FLUOTHANE is nonflam- apors mixed with oxygen rom 0.5 to 50 per cent plosive.

does not decompose in rm soda lime. When mois- , the vapor attacks alumi- nd lead, but not copper. s soluble in rubber, some imilar materials; such ma- teriorate rapidly in contact ANE vapor or liquid. Stabil- HANE is maintained by the 01 per cent thymol (w/w), s in amber colored bottles. NE should not be kept indefi- aporizing bottles not specifically ed for its use. It is recommended at vaporizers be emptied at the end of each operating day. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinepharine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE should be avoided when a previous exposure was followed by fever and jaundice, or when there was an unexplained postoperative fever.

FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy: Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

Adverse Reactions. The following adverse reactions have been reported: hepatic necrosis, cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide (usually in a 50:50 ratio).

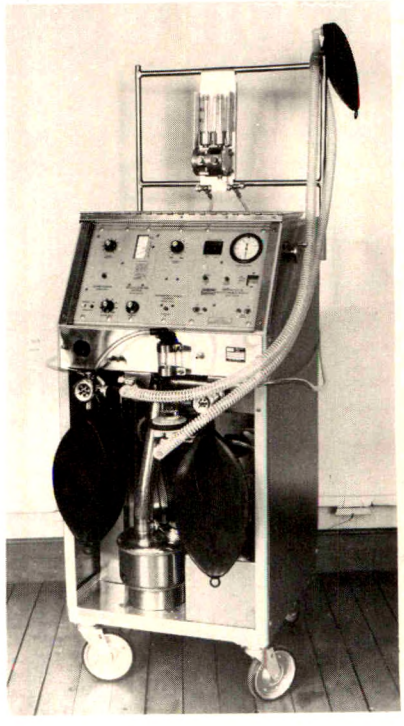
How Supplied. No. 3125—Unit packages of 125 cc. and 250 cc. of halothane stabilized with 0.01% thymol (w/w).

7522

Ayerst AYERST LABORATORIES
New York, N.Y. 10017

EMERSON IMV Ventilator

Intermittent Mandatory Ventilation



Continuous-flow voluntary ventilation, with intermittent forced breaths, is an alternative to assisted or controlled respiration. It has been found especially valuable for infants and for use in "weaning" adults as they improve.

Air fully humidified (and usually enriched with oxygen) flows continuously to a reservoir bag, and is available for unobstructed inspiration by the patient. A slight expiratory back-pressure (PEEP) may be added, to keep the lungs expanded. At intervals the ventilator delivers a "mandatory" breath, which supplements the patient's own breathing activity and increases minute volume. The machine does not have to "take over". The patient maintains his own homeostasis, without interference from drugs or hyperventilation.[1]

At first the ventilator is generally set to supply mandatory breaths at a normal controlled rate. This controlled respiration is then gradually changed, by lengthening the interval between breaths (a second or two at a time) as the patient's condition improves. Eventually mandatory breaths are spaced so far apart that the patient scarcely relies on them at all — and "weaning" is completed.[2]

VERSUS ASSIST

Triggering an assistor has often been a problem, particularly for infants, since their rates are rapid and their inspiratory impulses are slight. If synchronization is less than perfect, the patient inhales (at least part of the time) with no fresh gas available. Under such circumstances, blood levels of CO_2 rise, as noted by Kirby and associates.[1]

VERSUS CONTROL

For apneic patients, control is obviously needed. But to take over, when a patient is breathing spontaneously, drugs have to be used or the patient has to be hyperventilated. Either procedure has drawbacks. Paralytic or sedative agents may obscure signs of neurological or metabloic disorders. Lowered muscle tone may impair venous return, and hence cardiac output. The effects of such drugs are particularly hard to predict in infants.

Hyperventilation (often used to suppress spontaneous breathing efforts) has drawbacks, too. The resultant alkalosis reduces cerebral blood flow. Blood levels of calcium and magnesium are altered. Airway resistance increases and pulmonary compliance decreases with hypocarbia.[3] Finally, there is evidence of a shift in the carbon dioxide response curve, which makes weaning more difficult.

All of these pit-falls can be avoided by using continuous-flow IMV.

Please request Form 3-MV.

J. H. EMERSON COMPANY

CAMBRIDGE, MASSACHUSETTS 02140

Uncommon Endotracheal Tubes From The Most Commonly Known Name In Anesthesia

Now here's a disposable endo tube worthy of the OHIO name!

Uncuffed, or with anatomically designed cuffs for a gentle seal. Clear tubes, Murphy eye, radiopaque tips, depth markings. And a unique inflation and pilot balloon assembly.

OHIO now makes a wide range of sizes. Each tube, sterile packed, for one-patient use.

It's common knowledge that OHIO is the leader in anesthesia equipment. A dependable supplier of inhalation agents and medical gases.

Now, watch us move ahead in disposables. Endo tubes, an anesthesia breathing circuit, filters, masks, airways, suction valves, catheters, tubing . . . And more coming. With many distribution and delivery facilities to keep you supplied.

Write for Catalog # 2604. Or contact your OHIO representative about disposables. For the common good of you and your patients.

Ohio Medical Products

P. O. Box 1319, Dept. A&A
3030 Airco Drive
Madison, Wisconsin 53701

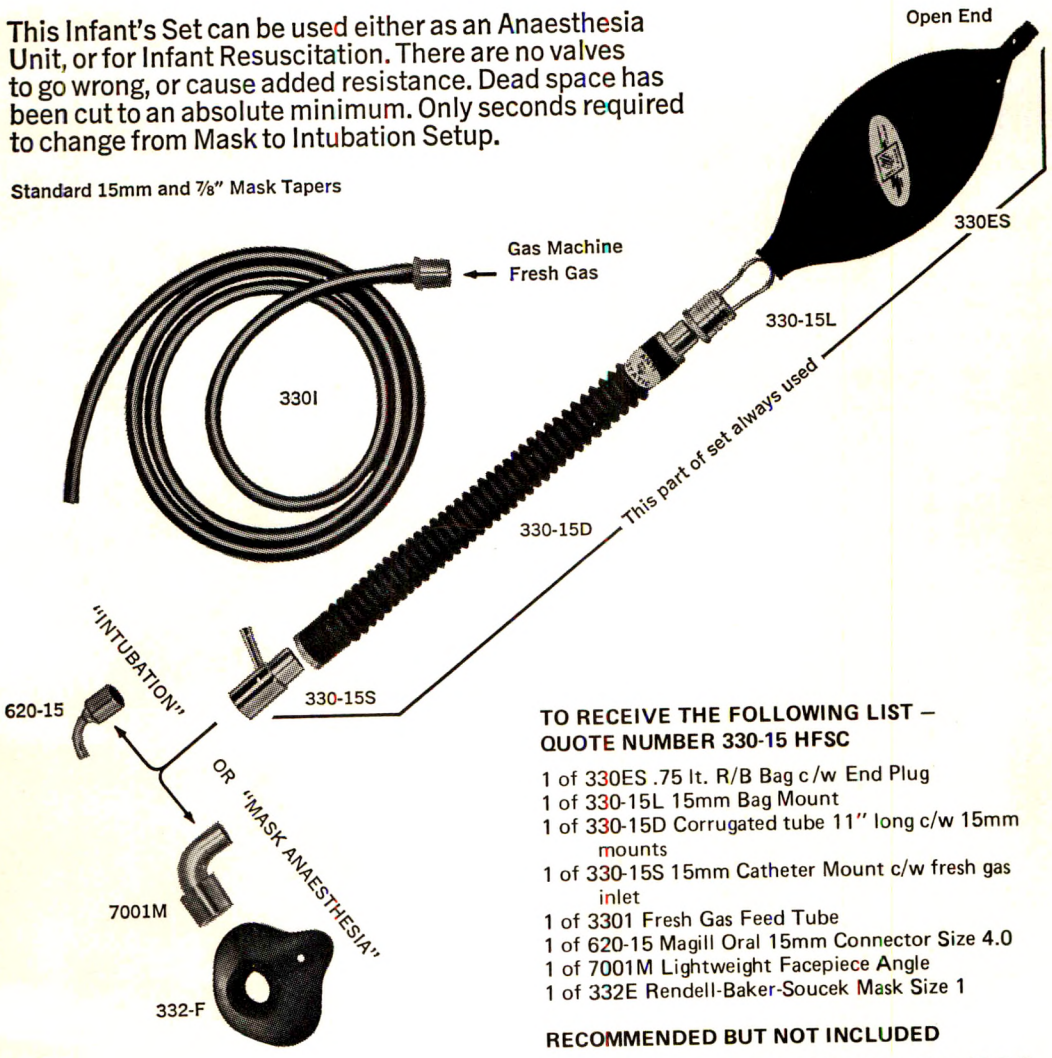
AIRCO®

JACKSON-REES MODIFICATION OF AYRE'S T-PIECE

as used by leading children's hospitals

This Infant's Set can be used either as an Anaesthesia Unit, or for Infant Resuscitation. There are no valves to go wrong, or cause added resistance. Dead space has been cut to an absolute minimum. Only seconds required to change from Mask to Intubation Setup.

Standard 15mm and 7/8" Mask Tapers



TO RECEIVE THE FOLLOWING LIST — QUOTE NUMBER 330-15 HFSC

1 of 330ES .75 lt. R/B Bag c/w End Plug
1 of 330-15L 15mm Bag Mount
1 of 330-15D Corrugated tube 11" long c/w 15mm mounts
1 of 330-15S 15mm Catheter Mount c/w fresh gas inlet
1 of 3301 Fresh Gas Feed Tube
1 of 620-15 Magill Oral 15mm Connector Size 4.0
1 of 7001M Lightweight Facepiece Angle
1 of 332E Rendell-Baker-Soucek Mask Size 1

RECOMMENDED BUT NOT INCLUDED

6 (1 each) 330CF Foregger Coles Tubes 8 to 18 F.G.
1 No. 332F Rendell-Baker-Soucek Mask Size 2
1 No. 332L Rendell-Baker-Soucek Mask Size 3
1 330LC Leather Case
1 of 330-15D Corrugated tube c/w 15mm mounts.

We recommend you purchase a 330LC Leather Case to store this equipment — prevents loss or damage.

MIE

MEDICAL & INDUSTRIAL EQUIPMENT
A division of Claudius Ash Incorporated
655 - 73rd Street, Niagara Falls, New York 14304

SEND FOR COMPLETE LITERATURE

ANECTINE®
(succinylcholine chloride)
For controlled muscle relaxation adjunctive to anesthesia:

FLO-PACK® for prolonged relaxation

- instant-mix sterile powder interfaces with all major parenteral systems (vacuum or nonvacuum)
- each unit complete—no needle or syringe needed
- retains potency indefinitely
- no refrigeration required
- unbreakable, sterile plastic injection units of 500 and 1,000 mg

INJECTION for short-term relaxation

- a product of choice for intubation and other short procedures
- unique square bottle and bright yellow label for positive identification
- ready for immediate use
- 20 mg per cc . . . in 10 cc multidose vials
- flip-top cap for easy opening
- single or multiple use

ANECTINE®
(succinylcholine chloride)
THE LONG AND SHORT of surgical muscle relaxation

THIS DRUG SHOULD BE USED ONLY BY INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS AND HAZARDS.

DESCRIPTION: Anectine brand Succinylcholine Chloride is an ultra short-acting depolarizing type muscle relaxant. Chemically it is a di-quaternary base consisting of the di-chloride salt of the di-choline ester of succinic acid. It is a white, odorless, slightly bitter powder and very soluble in water. The drug is unstable with alkaline solutions, but relatively stable in acid solutions depending upon the concentration of the solution and the storage temperature. While solutions of succinylcholine chloride are sterilized by autoclaving, they should, nevertheless, be stored under refrigeration to preserve their potency.

INDICATIONS: Succinylcholine chloride is indicated as an adjunct to anesthesia to induce skeletal muscle relaxation. It may be employed to reduce the intensity of muscle contractions of pharmacologically or electrically induced convulsions.

CONTRAINDICATIONS: Succinylcholine is contraindicated for persons with a known hypersensitivity to the drug.

WARNINGS:

WARNING: SUCCINYLCHOLINE SHOULD BE USED ONLY BY THOSE SKILLED IN THE MANAGEMENT OF ARTIFICIAL RESPIRATION AND ONLY WHEN FACILITIES ARE INSTANTLY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND FOR PROVIDING ADEQUATE VENTILATION OF THE PATIENT, INCLUDING THE ADMINISTRATION OF OXYGEN UNDER POSITIVE PRESSURE AND THE ELIMINATION OF CARBON DIOXIDE., THE CLINICIAN MUST BE PREPARED TO ASSIST OR TO CONTROL RESPIRATION.

Succinylcholine should not be mixed with short-acting barbiturates in the same syringe, or administered simultaneously during intravenous infusion through the same needle. Solutions of succinylcholine have an acid pH whereas those of barbiturates are alkaline in reaction. Depending upon the resultant pH of a mixture of solutions of these drugs, either free barbituric acid may be precipitated or succinylcholine hydrolyzed.

Usage in Pregnancy The safe use of succinylcholine has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

PRECAUTIONS: Low levels of, or abnormal variants of plasma cholinesterase may be associated with prolonged respiratory depression or apnea following the use of succinylcholine. Low levels of plasma cholinesterase may occur in patients with severe liver disease or cirrhosis, severe anemia, malnutrition, severe dehydration, changes in body temperature, exposure to neurotoxic insecticides or those receiving antimalarial drugs. Succinylcholine should be administered with extreme care to such patients and dosage should be minimal. If low plasma cholinesterase activity is suspected, a small test dose of from 5 to 10 mg of succinylcholine may be administered, or relaxation may be produced by the cautious administration of a 0.1% solution of the drug by intravenous drip. Drugs which either inhibit plasma cholinesterase, such as neostigmine or phospholine iodide, or compete with succinylcholine for the enzyme, as does intravenous procaine, should not be given concurrently with succinylcholine.

Succinylcholine should be administered with great caution to patients with severe burns, those recovering from severe trauma, those suffering from electrolyte imbalance, those receiving quinidine, those who have been digitalized recently or who may have digitalis toxicity as serious cardiac arrhythmias or cardiac arrest may result. Great caution should be observed also in patients with pre-existing hyperkalemia or who are paraplegic, have suffered spinal neuraxis injury, or have degenerative or dystrophic neuromuscular disease, as such patients tend to become severely hyperkalemic when succinylcholine is given.

When succinylcholine is given over a prolonged period of time, the characteristic depolarization block of the myoneural junction may change to a non-depolarizing block which results in prolonged respiratory depression or apnea. Under such circumstances, small repeated doses of neostigmine may possibly act as an antagonist. A peripheral nerve stimulator (e.g., the Wellcome Peripheral Nerve Stimulator) may be used to ascertain the type of neuromuscular blockade. If a depolarization block is present both fast (tetanic) and slow (twitch) rates of nerve stimulation are well sustained, and post-tetanic facilitation is absent. If a non-depolarizing block is present there is post-tetanic facilitation and "fade" of successive stimuli on both fast (tetanic) and slow (twitch) rates of nerve stimulation.

Succinylcholine should be used with caution during ocular surgery and in patients with glaucoma. The drug should be employed with caution in patients with fractures or muscle spasm as the muscle fasciculations may cause additional trauma. Muscle fasciculations and hyperkalemia may be reduced by administering a small dose of a non-depolarizing relaxant. If other relaxants are to be used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered.

During the past few years, reports have called attention to a fulminant syndrome, malignant hyperthermia, observed during anesthesia. Its etiology is not fully understood. Malignant hyperthermia occurs in genetically prone individuals of all ages and both sexes receiving potent anesthetics such as halothane, methoxyfluorothane, cyclopropane and diethyl ether. It appears to develop irrespective of the concomitant use of a muscle relaxant, but may be triggered by succinylcholine. Because of the seriousness of this syndrome and the need for early effective treatment of the patient, it is suggested that the continuous monitoring of the temperature will serve as an aid to the early recognition of malignant hyperthermia.

ADVERSE REACTIONS: Adverse reactions consist primarily of an extension of the drug's pharmacological actions. Profound and prolonged muscle relaxation may occur, resulting in respiratory depression to the point of apnea. Hypersensitivity to the drug may exist in rare instances.

The following adverse reactions have been reported: bradycardia, tachycardia, hypertension, hypotension, arrhythmias, cardiac arrest, prolonged respiratory depression or apnea, hyperthermia, increased intraocular pressure, muscle fasciculation, postoperative muscle pain, myoglobinemia and excessive salivation.

MANAGEMENT OF ADVERSE REACTIONS: Apnea or prolonged muscle paralysis should be treated with controlled respiration.

The use of neostigmine to reverse a non-depolarization block is a medical decision which must be made upon the basis of the individual clinical pharmacology and the experience and judgment of the clinician. When neostigmine is used atropine should also be administered.

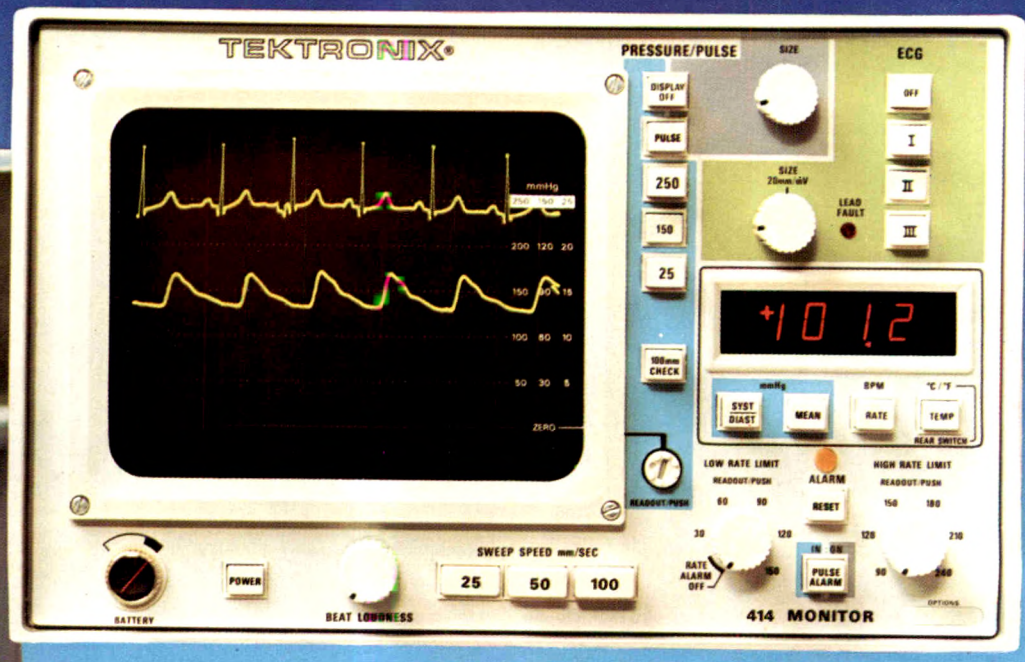
SUPPLIED: Injection, Multi-dose vials, 20 mg cc, 10 cc, boxes of 12 vials. Flo-Pack® Sterile Powder 500 mg and 1,000 mg, boxes of 12.

Complete literature available on request from Professional Services Dept. PML.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

Introducing the most complete monitor capability in a single compact instrument.



NEW Tektronix 414 Portable Patient Monitor

ECG. Temperature. Arterial, venous or pulmonary wedge pressure. Peripheral pulse. Only Tektronix 414 offers every feature for monitoring these vital signs—all neatly packaged in a single, portable unit. For increased accuracy and convenience, the 414 gives digital readout of heart rate, systolic/diastolic blood pressures, mean blood pressure, or temperature. Rate alarm limits are also set digitally.

And because the 414 permits cordless (battery) operation, it can be as easily used for cardiac catheterization as for surgery and recovery. Weight of a fully equipped 414 is approximately 12 lbs.

For more information or a demonstration of any of Tektronix Portable Patient Monitors in your facility, please write to Tektronix, Inc., P.O. Box 500, Beaverton, Oregon 97077. *Or call collect:* (503) 644-0161, extension 6510.

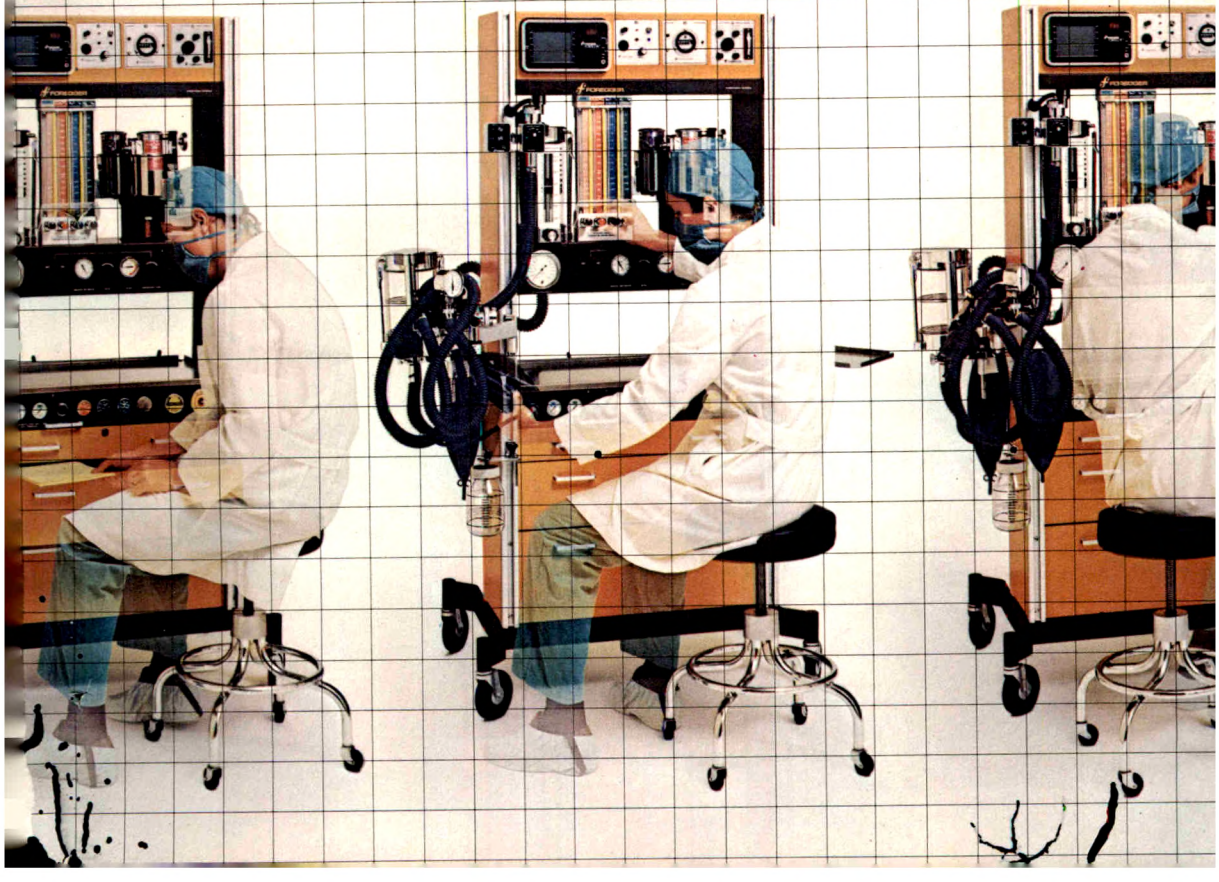
Excellence in Patient Monitoring

TEKTRONIX®
committed to technical excellence

P24572

Introducing The Human-Engineered Anesthesia Control Center.

The FOREGGER® 710



The FOREGGER 710 Anesthesia Control Center. Unlike Anything You've Ever Seen.

Think of what it is like using a typical anesthesia machine. Now, look at the new FOREGGER 710 Anesthesia Control Center. Notice the completeness, compactness, accessibility and visibility of the components. Everything is in one place, within reach . . . without dangling wires and add-on components. That's why we call it the FOREGGER 710 Anesthesia Control Center.

Unlike existing anesthesia machines, the FOREGGER 710 Anesthesia Control Center is human engineered. The design revolves around you. All of the controls for both fixed and movable components are operated from a comfortable, working position. And this ease of control is complemented by the latest innovations in anesthesia equipment design.

Take, for instance, the unique rotating Vaporizer Turret. It accommodates up to three vaporizers, including the Foregger Copper Kettle® Vaporizer and Foregger Direct Reading Vaporizers. When the Turret is locked into place, there is no doubt which vaporizer is in circuit. Possible contamination from anesthetic agents contained in the other vaporizers is eliminated.

Then there are the Direct Reading Vaporizers designed for the administration of a specific liquid anesthetic, over a wide range of temperatures and flow rates. The Copper Kettle Vaporizer, on the other hand, affords you constant and precise control in both increments and decrements, while providing simple and accurate administration of an anesthetic agent.

There's also a built-in Anesthesia Ventilator that features fluidic circuitry, independent controls, and a mode selector switch that enables you to transfer from ventilator to bag without changing tubes or adjusting the pressure relief valve. It gives you the convenience of easy readouts and the efficiency of direct control. And it's easy to clean.

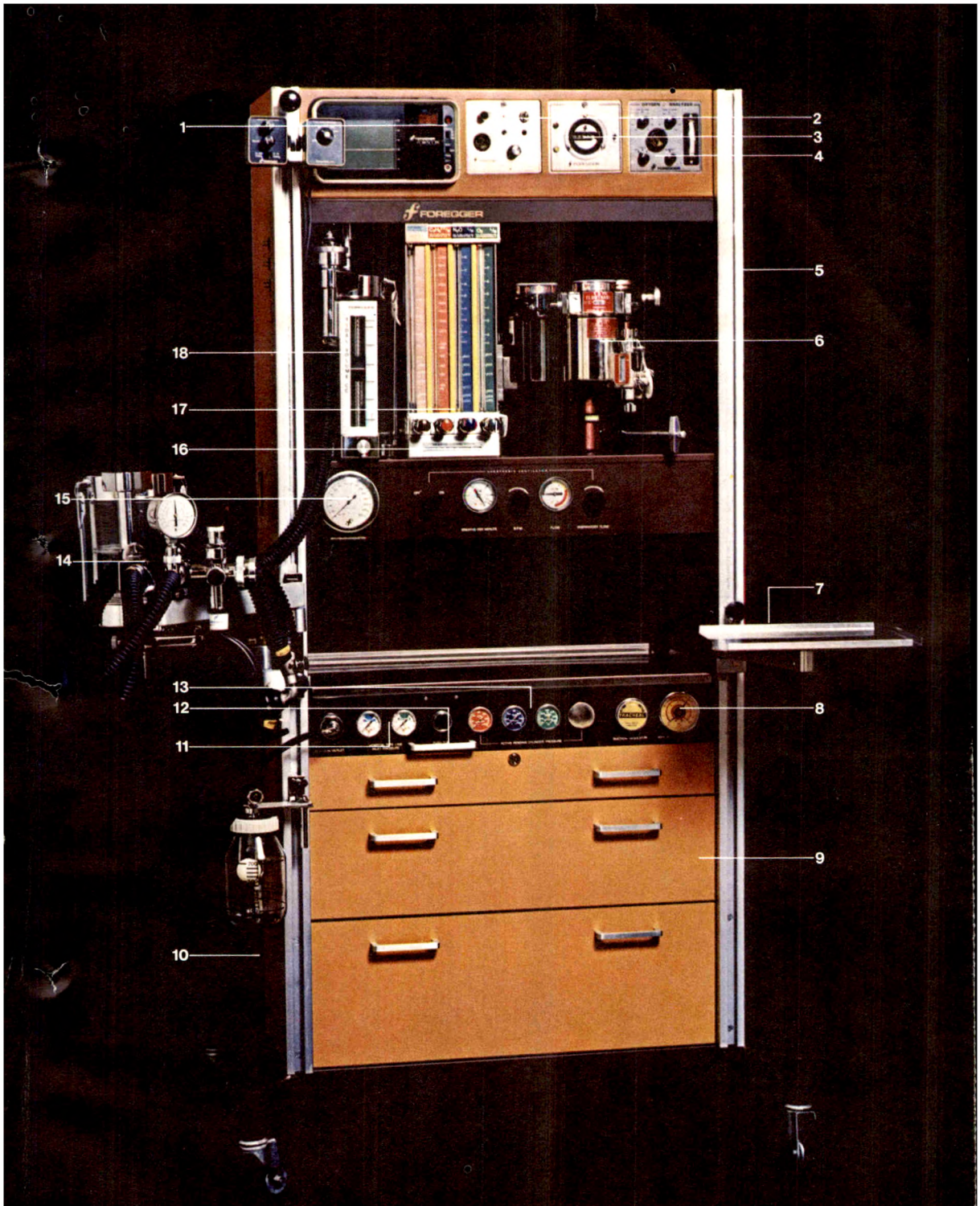
Storage is human-engineered too! Cabinetry in the new FOREGGER 710 Anesthesia Control Center combines linear designed storage with easy accessibility and large capacity.

The Monitoring System, which provides a wide range of physiological monitoring capability, is located where you need it during procedures. Easy to see and reach, it includes a physiological monitor (ECG, EEG, temperature, pulse rate, and pressure), an Oxygen Analyzer, Ventilator Disconnect Alarm, and an Elapsed Timer.

In addition, the FOREGGER 710 Anesthesia Control Center has a built-in Oxygen Start, which automatically shuts off all other gases when the oxygen flow is reduced to a predetermined level. Plus, four parallel accessory tracks to mount and adjust FOREGGER 710 Anesthesia Control Center accessories. All of which add another dimension to overall flexibility.

And that's where you should place the new FOREGGER 710 Anesthesia Control Center. Over all. In capabilities. Flexibilities. And human engineering. Take a look at its other unlike features and we think you'll agree . . . The FOREGGER 710 Anesthesia Control Center is unlike anything you have seen before. For more information about what human engineering with everything in one place can mean to you, fill out and return the attached card.

With FOREGGER—It's The Unlikely Things About Us That You'll Like.



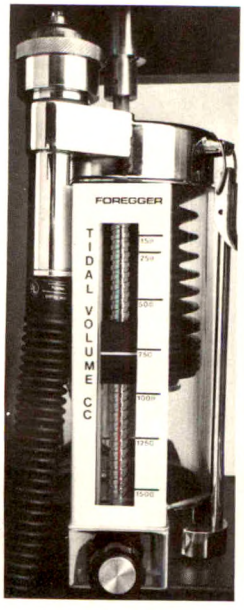
1. Physiological Monitor
2. Ventilator Alarm
3. Elapsed Timer
4. Oxygen Analyzer
5. Accessory Tracks
6. Vaporizer Turret
7. Writing/Record Table
8. Suction Canister and Regulator
9. Storage Section
10. Gas Evacuator
11. Hospital Pipeline Inlet Pressure Gauges
12. Oxygen Flush
13. Reserve Cylinder Pressure Gauges
14. Absorber
15. Sphygmomanometer
16. Oxygen Start
17. Color-Coded Flowmeters
18. Anesthesia Ventilator

The FOREGGER 710

Anesthesia Control Center.

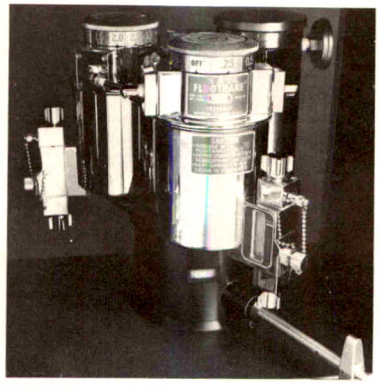
Everything Built-In, Not Added-On.

1

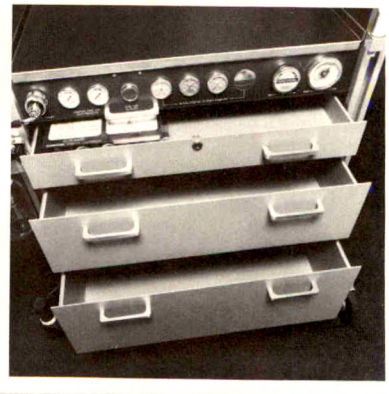


1) Built-In Ventilator
2) Vaporizer Turret
3) Deep-Dish Storage
4) Oxygen Start
5) Accessory Tracks
6) Patient Monitoring Console
   a) ECG, EEG, Temperature, Pulse Rate, Pressures
   b) Ventilator Disconnect Alarm
   c) Elapsed Timer
   d) Oxygen Analyzer

2

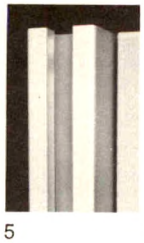


3



6

4



5

Safety Features

Incorporates many of the latest safety standards as recommended by the Z-79/CGA

Service from one source

Vaporizer Turret
Oxygen Analyzer
Ventilator Disconnect Alarm
Patient Monitoring
Low Pressure Guardian® System

Human engineered for optimal accessibility and visibility of components

Efficient Gas Evacuator

Oxygen Start System

Air Products
FOREGGER®

PEOPLE AND PLACES

"Anesthesia and the Respiratory System" is the title of the Fourth Annual Anesthesiology Review Course to be held February 28-29, 1976, by the Department of Anesthesiology and the Division of Continuing Medical Education of the University of Alabama in Birmingham with the co-sponsorship of the Alabama State Society of Anesthesiologists.

This Review Course is designed to survey concepts in the management of respiratory problems likely to be encountered in anesthetic practice. The program is clinically oriented in its entirety.

On Friday, February 27, and Monday, March 1, 1976, arrangements have been made for participants in the Review Course to observe anesthetic procedures, respirator demonstrations, nerve blocks, etc., at the UAB Medical Center. There will also be an opportunity for group discussions.

For more information, write to: Review Course, c/o Department of Anesthesiology, University of Alabama Medical Center, University Station, Birmingham, Alabama 35294.

* * *

The First Annual Vail Conference in Respiratory Therapy sponsored by the Department of Anesthesiology, University of Miami, Miami, Florida, will be held at the Lion Square Lodge in Vail, Colorado, February 28 - March 6, 1976.

* * *

The Obstetric Anaesthetists' Association in the United Kingdom will hold their next meeting in the University of Nottingham on March 26, 1976. **Dr. B. A. Waldron,** Consultant Anaesthetist, Nottingham City Hospital, Hucknall Road, Nottingham, will be the host for this meeting.

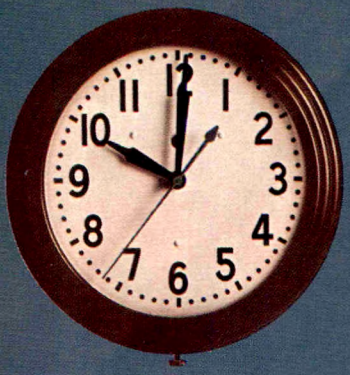
Their following meeting will be on September 24, 1976, in the University of South Manchester. All people wishing to present a paper at the Manchester meeting should write to **Dr. Valerie Hey,** Withington Hospital, West Didsbury, Manchester, before May 1, 1976.

* * *

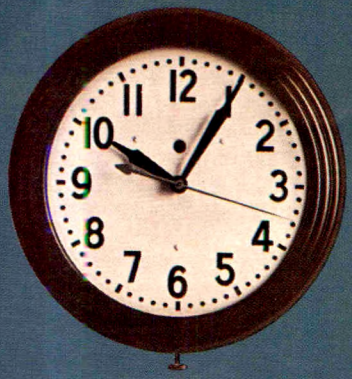
The Connecticut State Society of Anesthesiologists will present the 9th Biennial Connecticut Postgraduate Seminar in Anesthesiology at the Hunt Memorial Auditorium of the Hartford Medical Society Building, 230 Scarborough Street in Hartford, Connecticut, on Friday, May 7, and Saturday, May 8, 1976. The subject is "Clinical Problems in Anesthesia." Details may be obtained from **James C. Rouman, MD,** Chairman, Postgraduate Education Committee, 85 Jefferson Street, Suite 407, Hartford, Connecticut 06106.

* * *

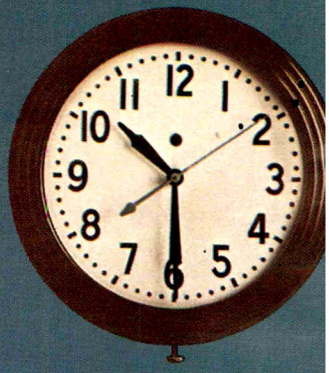
Dr. M. Digby Leigh, a long-time friend of many of us, died September 5, 1975, in Palm Springs, California. Doctor Leigh was certified in Anaesthesia by the Royal College of Physicians, Canada, and by the American Board of Anesthesiology. He was the chief author of two editions of *Pediatric Anesthesiology,* 1948 and 1960, and of numerous articles. He devised several pieces of anesthetic equipment, most notably the non-rebreathing valve and the infant circle filter. His students and associates knew him as a superb teacher and shrewd clinician, as well as an inspiring and demanding, but very much respected and admired "Chief."



SUBLIMAZE® (fentanyl) has a uniquely short duration of analgesic action—for more precise control and minimal risk of prolonged narcotic effects.

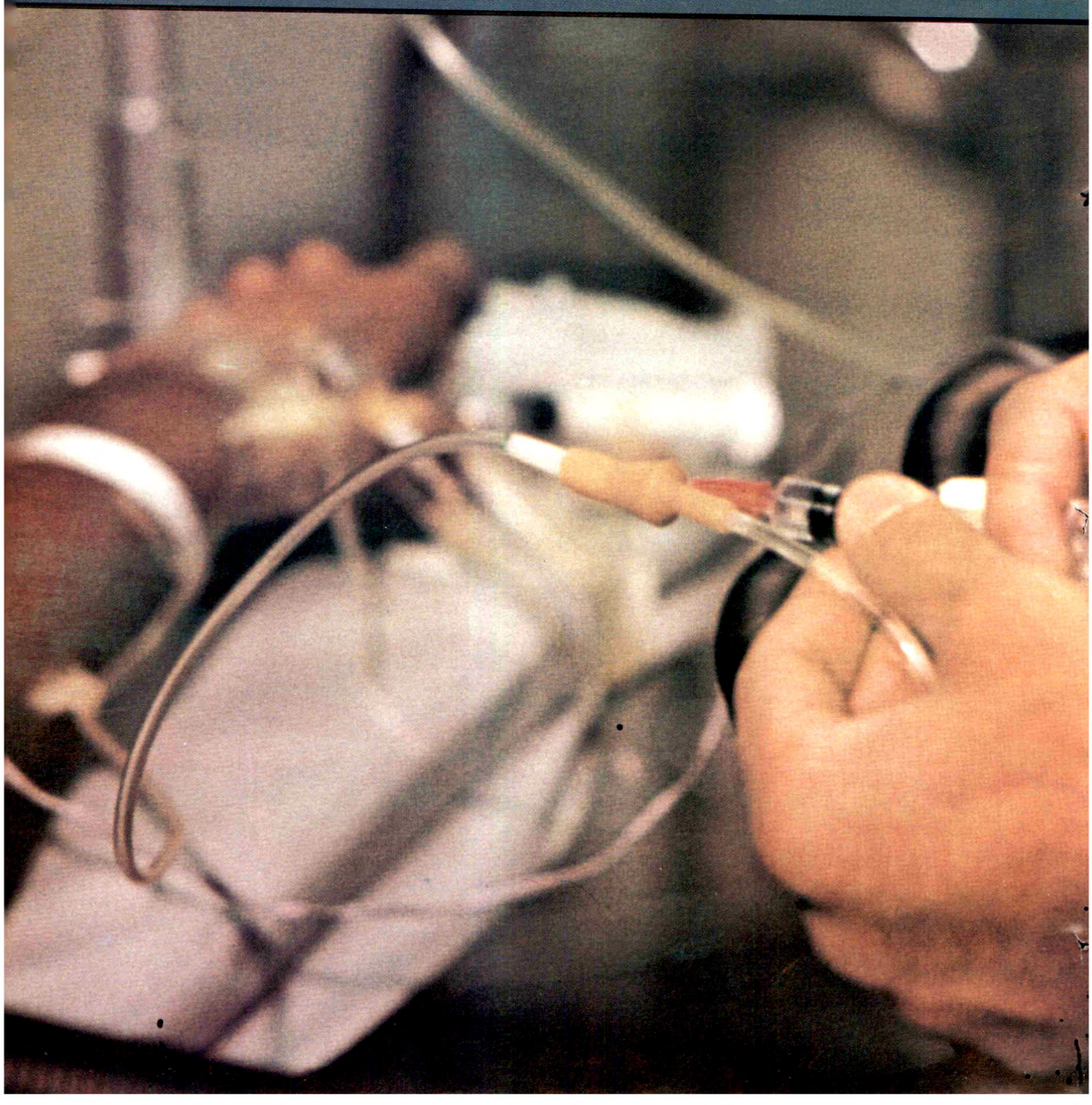


Within 5 minutes I.V., SUBLIMAZE® (fentanyl) reaches its peak analgesic effect.



Within 30 to 60 minutes I.V., the analgesic effect of SUBLIMAZE® (fentanyl) is almost completely dissipated.†

† Respiratory depressant effects may last longer than the analgesia and are increased and prolonged with larger doses, multiple doses or use of postoperative narcotic analgesics.



For potent narcotic analgesic action with rapid onset and short duration:

SUBLIMAZE fentanyl provides profound analgesia without hypnosis and with little or no sedation. With this analgesia as a foundation, it is possible to use light general anesthesia in most cases.

SUBLIMAZE fentanyl is particularly suited for maintenance of analgesia after INNOVAR® injection* has been used for induction. It may also be used preoperatively, during surgery with any common general or regional anesthetic agent, and in the immediate postoperative period whenever the need for potent analgesic action arises.

SUBLIMAZE fentanyl is available both alone and as a component of INNOVAR injection.*

*INNOVAR injection is composed of a 50:1 mixture of droperidol 2.5 mg./cc. and fentanyl 0.05 mg./cc., with lactic acid for adjustment of pH to 3.5 ± 0.3.

SUBLIMAZE® (fentanyl) offers:

☐ Almost immediate analgesia—peak effect within 5 minutes I.V., 8 minutes I.M.

☐ Short duration of analgesic action—30 to 60 minutes with a single I.V. dose of up to 0.1 mg. (Respiratory depressant effects may last longer than the analgesia and are increased and prolonged with larger doses, multiple doses or use of postoperative narcotic analgesics.)

☐ No evidence of liver, heart, or kidney toxicity—expecially valuable in poor-risk patients. However, the drug should be administered cautiously in the presence of liver or kidney dysfunction or cardiac arrhythmias, and the dose should be appropriately reduced in poor-risk patients.

☐ Immediate reversibility by narcotic antagonists.

☐ Little or no histamine release—decreasing the risk of cardiovascular instability.

☐ Minimal emetic effect—has been used successfully to prepare nonfasting patients for awake intubation.

☐ Prevention or reversal of emergence delirium and tachypnea.

SUBLIMAZE® Ⓒ Ⅱ (fentanyl) injection

0.05 mg./cc. as the citrate.
Warning: May be habit forming.
Sodium hydroxide for adjustment of pH to 4.0—7.5

INNOVAR® injection and SUBLIMAZE® (fentanyl) injection are available for use only upon direction of a physician. For information relating to Contraindications, Warnings, Precautions and Adverse Reactions for SUBLIMAZE fentanyl, please turn page.

© McNeil Laboratories, Inc., 1974

SUBLIMAZE® (fentanyl) injection

Description
Each cc. contains:
Fentanyl as the citrate . . . . . 0.05 mg.
Warning—May be habit forming.
Sodium hydroxide for adjustment of pH to 4.0–7.5
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY.

Actions SUBLIMAZE fentanyl is a narcotic analgesic with actions qualitatively similar to those of morphine and meperidine. SUBLIMAZE fentanyl in a dose of 0.1 mg. (2.0 cc.) is approximately equivalent in analgesic activity to 10 mg. of morphine or 75 mg. of meperidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. SUBLIMAZE fentanyl appears to have less emetic activity than other narcotic analgesics. Histamine assays and skin wheal testing in man, as well as *in vivo* testing in dogs, indicate that histamine release rarely occurs with SUBLIMAZE fentanyl.

SUBLIMAZE fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. It may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia, and bronchoconstriction.

The onset of action of SUBLIMAZE fentanyl is almost immediate when the drug is given intravenously; however, maximal analgesic and respiratory depressant effect may not be noted for several minutes. The average duration of action of the analgesic effect is 30 to 60 minutes. Following intramuscular administration, the onset of action is from seven to eight minutes, and the duration of action is from one to two hours.

Although the duration of the respiratory depressant effect is unknown, as with other narcotic analgesics it may be considerably longer than the analgesic effect.

Indications SUBLIMAZE fentanyl is indicated:
—for analgesic action of short duration during the anesthetic periods, premedication, induction, and maintenance, and in the immediate postoperative period (recovery room) as the need arises.
—for use as a narcotic analgesic supplement in general or regional anesthesia.
—for administration with a neuroleptic such as INAPSINE® (droperidol) injection as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.

Contraindications SUBLIMAZE fentanyl is contraindicated in patients who are hypersensitive to the drug.

Warnings PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* FENTANYL SHOULD HAVE APPROPRIATE SURVEILLANCE, RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

If SUBLIMAZE fentanyl is administered with a tranquilizer such as INAPSINE droperidol, the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE fentanyl persists longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as 1/4 to 1/3 those usually recommended. A neuromuscular blocking agent compatible with the patient's condition may be required to control muscle rigidity which may develop with the use of SUBLIMAZE fentanyl.

Drug Dependence: SUBLIMAZE fentanyl can produce drug dependence of the morphine type and therefore has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE fentanyl in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure: SUBLIMAZE fentanyl should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition, SUBLIMAZE fentanyl may obscure the clinical course of patients with head injury.

Usage in Children: The safety of SUBLIMAZE fentanyl in children younger than two years of age has not been established.

Usage in Pregnancy: The safe use of SUBLIMAZE fentanyl has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

Precautions *The initial dose of SUBLIMAZE fentanyl should be appropriately reduced in elderly, debilitated and other poor risk patients. The effect of the initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms (see Actions) SUBLIMAZE fentanyl can also alter respiration. When SUBLIMAZE fentanyl is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia. When used with a tranquilizer such as INAPSINE droperidol, blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE fentanyl should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Postoperatively, respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists (levallorphan, nalorphine, and naloxone; consult individual prescribing information before using). Should respiration be compromised by muscle rigidity, assisted or controlled respiration and possibly a neuromuscular blocking agent will be required. The occurrence of muscle rigidity is related to the speed of intravenous injection and the incidence can be reduced by slow intravenous injection.

When a tranquilizer such as INAPSINE droperidol is used with SUBLIMAZE fentanyl, pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE fentanyl. When patients have received such drugs, the dose of SUBLIMAZE fentanyl required will be less than usual. Likewise, following administration of SUBLIMAZE fentanyl the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE fentanyl should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE fentanyl may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE fentanyl should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE fentanyl is used with a tranquilizer such as INAPSINE droperidol, hypotension can occur. If this occurs the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of INAPSINE droperidol, epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE droperidol.

Adverse Reactions As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE fentanyl are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur.

Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

When a tranquilizer such as INAPSINE droperidol is used with SUBLIMAZE fentanyl, the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with antiparkinson agents. Postoperative drowsiness is also frequently reported following the use of INAPSINE droperidol.

Overdosage ***Manifestations:*** The manifestations of SUBLIMAZE fentanyl overdosage are an extension of its pharmacologic actions.
Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan, or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. Consult the package insert for the individual narcotic antagonists for details about use.

How Supplied SUBLIMAZE® (fentanyl) injection is supplied in 2 cc. (**NDC** 0045-0180-03) and 5 cc. (**NDC** 0045-0180-05) ampuls, in packages of 12.

IMPORTANT: Complete dosage information is available in insert which accompanies each package (or on request). The drug is available only upon direction of a physician.

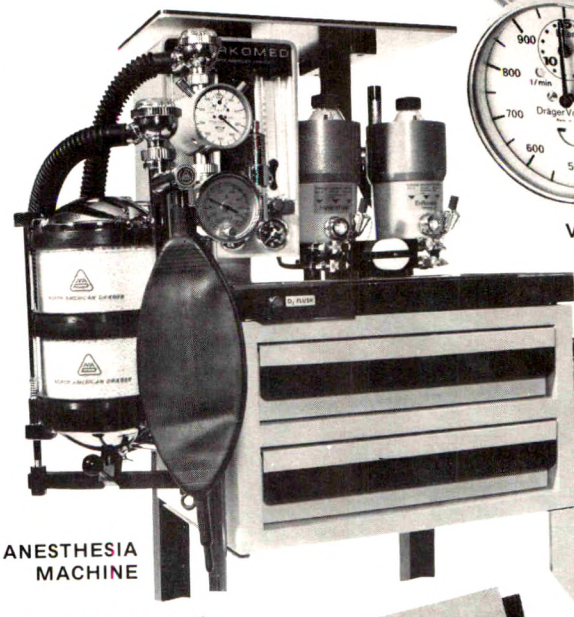
U.S. Patent No. 3,164,600

9/74

McNEIL McNeil Laboratories, Inc.
Fort Washington, Pa. 19034

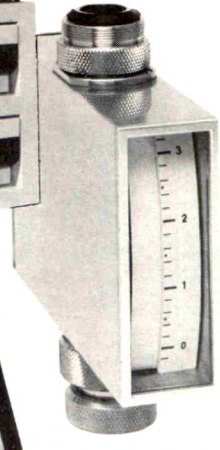
All Drager

VAPORIZER



ANESTHESIA MACHINE

VOLUMETER



ANESTHESIA ANALYZER

VAPOR VAPORIZER — Outstanding accuracy at flow rates ranging from 0.3 l/min. to 12 l/min. Back pressure compensated. Available for Halothane, Enflurane, Methoxyflurane & Ether.

NARKOTEST-M ANESTHESIA ANALYZER — Fits all current anesthesia absorbers or can be mounted on a portable stand. Provides in-line continuous reading of inspired Halothane concentrations. The NARKOTEST can also be used to measure expiratory values of various anesthetic agents.

MINUTE VOLUMETER 2000 — Measures both minute volume and tidal volume. A built-in timer will actuate the measuring mechanism for one minute and store the result until cancelled, or the unit can be used to continuously measure tidal volumes. Moisture or the composition of measured gas will not affect the unit. It can be mounted on most anesthesia absorbers and ventilators, or used portably.

NARKOMED ANESTHESIA MACHINE — A refreshing new dimension in anesthesia design and styling — NARKOMED — a modular anesthesia breathing system designed to include the widest variety of options.

NORTH AMERICAN DRÄGER

TELFORD, PENNSYLVANIA 18969
TELEPHONE: 215-723-9824

NORTH AMERICAN DRÄGER

P.O. Box 121
Telford, Pa. 18969

☐ Please send information on _____

☐ Include copy of new Anesthesia Accessories Catalog. (Coupon copy)

NAME _____

TITLE _____

HOSPITAL _____

ADDRESS _____

STATE _____ ZIP _____

ANTILIRIUM
(Physostigmine Salicylate)

REVERSES MOST POST-OPERATIVE DELIRIUM AND PROLONGED SOMNOLENCE

Before prescribing, please consult complete product information, a summary of which follows:

ACTION: ANTILIRIUM (physostigmine salicylate) is a salicylic acid derivative of an alkaloid extracted from seeds of Physostigma Venenosum (calabar bean). The action of the parasympathetic nerves is intermediated by the formation of acetylcholine at the peripheral end of these nerves. Physostigmine inhibits the destructive action of cholinesterase and thereby prolongs and exaggerates the effect of the acetylcholine.

Physostigmine contains a tertiary amine and easily crosses the blood brain barrier, while neostigmine contains a quaternary amine and is not capable of crossing the structure. This may explain why neostigmine does not cause reversal of anticholinergic-induced delirium while physostigmine does.

INDICATIONS: TO REVERSE THE TOXIC EFFECTS UPON THE CENTRAL NERVOUS SYSTEM CAUSED BY DRUGS IN CLINICAL OR TOXIC DOSAGES CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING.

SEVERE ANTICHOLINERGIC POISONING MAY PRODUCE: COMA, MEDULLARY PARALYSIS AND DEATH.

CENTRAL TOXIC EFFECTS MAY INCLUDE: HALLUCINATIONS, DELIRIUM, DISORIENTATION, ANXIETY AND HYPERACTIVITY.

Dramatic reversal within minutes of coma, hallucinations, and other signs can be expected if the diagnosis is correct and the patient has not suffered anoxia or other insult. Therapeutic doses may be necessary at intervals as life-threatening signs recur. Physostigmine is destroyed in the body in 60 to 120 minutes.

CONTRAINDICATIONS: Physostigmine should not be used in the presence of asthma, gangrene, diabetes, cardiovascular disease, mechanical obstruction of the intestines or urogenital tract or any vagotonic state, and in patients receiving choline esters or depolarizing neuromuscular blocking agents.

WARNING: If excessive symptoms of salivation, emesis, urination and defecation occur, the use of ANTILIRIUM should be terminated. If excessive sweating or nausea occur, the dosage should be reduced.

Intravenous administration should be at a slow, controlled rate, no more than 1 mg. per minute (see dosage). Rapid administration can cause bradycardia, hypersalivation leading to respiratory difficulties and possibly convulsions.

An overdosage of ANTILIRIUM can cause a cholinergic crisis.

PRECAUTIONS: Because of the possibility of hypersensitivity in an occasional patient, atropine sulfate injection should always be at hand since it is an antagonist and antidote for physostigmine.

ADMINISTRATION AND DOSAGE: The usual adult dose of ANTILIRIUM is 0.5 to 2.0 mg. intramuscularly or intravenously. Intravenous administration should be at a slow, controlled rate of no more than 1 mg. per minute. It may be necessary to repeat dosages of 1 mg. to 4 mg. at intervals as life threatening signs such as arrhythmias, convulsions and deep coma recur.

IN ALL CASES OF POISONING, THE USUAL SUPPORTIVE MEASURES SHOULD BE UNDERTAKEN.

SUPPLIED: 2 ml. ampules containing: PHYSOSTIGMINE SALICYLATE 1 mg. per ml. Packed 12 ampules per box.

NDC 0456-1037-12

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES:

Greene, L. T.: Physostigmine treatment of anticholinergic drug depression in postoperative patients. Anesth & Analg, March-April 1971; 50-2: 222-226.

Rumack, B.: Anticholinergic poisoning: Treatment with physostigmine. Pediatrics, Sept. 1973.

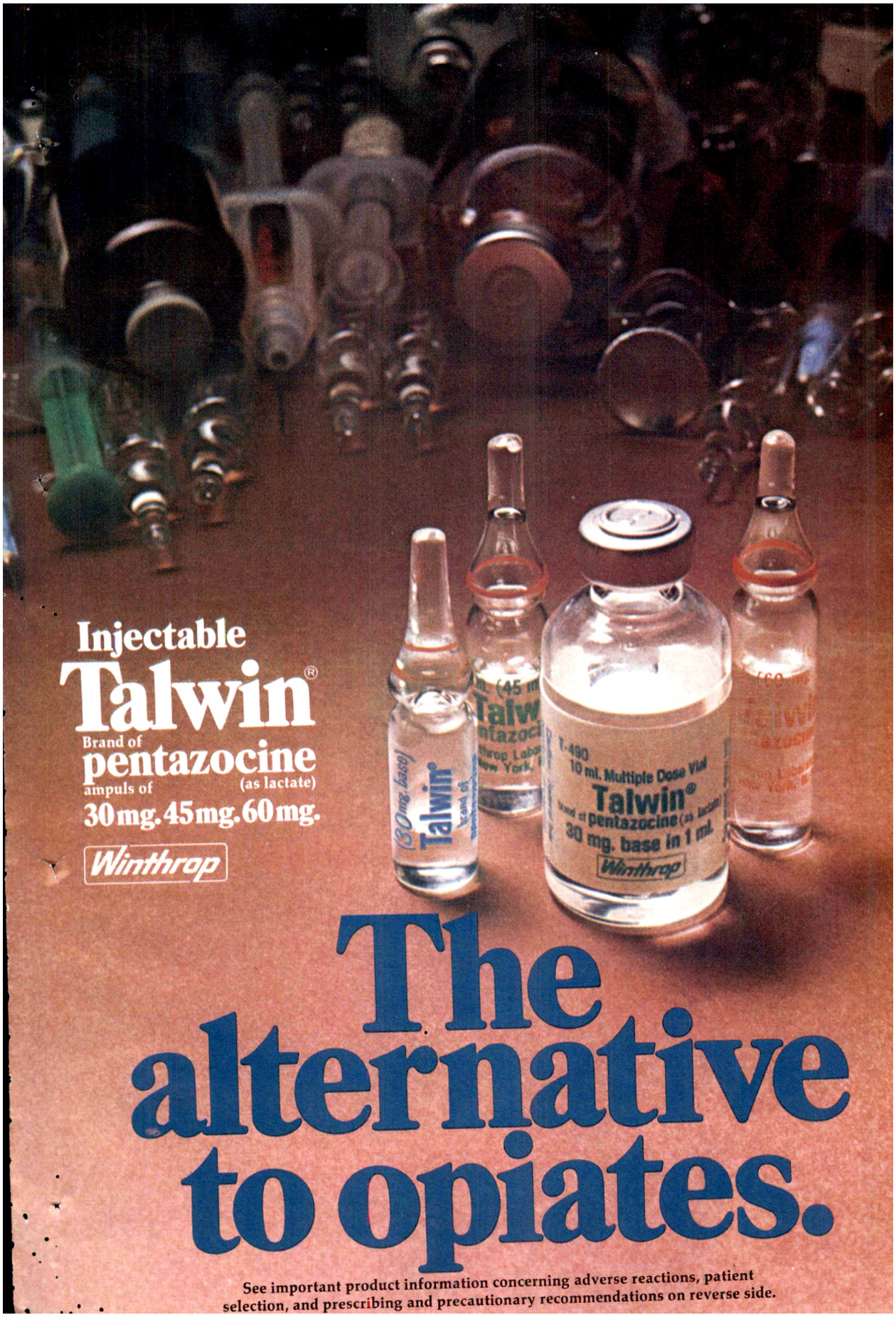
Slovis, T. L., Ott, J. E., Tietelbaum, D. T., and Lipscomb, W.: Physostigmine therapy in acute tricyclic antidepressant poisoning. Clinical Toxicology, 4:451, 1971.

DRUGS AND CHEMICALS CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING:

- AMITRIPTYLINE (Elavil, Triavil, Etrafon)
- ANISOTROPINE METHYLBROMIDE
- ATROPINE
- BELLADONNA
- BENACTYZINE
- CHLORPHENIRAMINE
- CYCLOPENTOLATE
- DESIPRAMINE (Norpramin, Pertofrane)
- DICYCLOMINE
- DIPHENHYDRAMINE
- DOXEPIN (Sinequan)
- HOMATROPINE
- HYOSCINE
- HYOSCYAMUS
- IMIPRAMINE (Tofranil, Presamine)
- ISOPROPAMIDE
- MEPENZOLATE
- METHANTHELINE
- METHAPYRILENE
- NORTRIPTYLINE (Aventyl)
- PIPENZOLATE BROMIDE (Piptal)
- PROPANTHELINE
- PROTRIPTYLINE (Vivactil)
- PYRILAMINE
- SCOPOLAMINE
- STRAMONIUM
- PHENOTHIAZINES
- TRICYCLIC ANTIDEPRESSANTS (Aventyl, Elavil, Etrafon, Norpramin, Pertofrane, Presamine, Tofranil, Triavil, Vivactil)
- THIORIDAZINE (Mellaril)

O'NEAL, JONES & FELDMAN, INC.

1304 ASHBY ROAD • ST. LOUIS, MISSOURI 63132 • (314) 997-6650


Injectable
Talwin®
Brand of
pentazocine
ampuls of (as lactate)
30 mg. 45 mg. 60 mg.
Winthrop
Talwin®
T-490
10 ml. Multiple Dose Vial
Talwin®
pentazocine (as lactate)
30 mg. base in 1 ml.
Winthrop
The alternative to opiates.
See important product information concerning adverse reactions, patient selection, and prescribing and precautionary recommendations on reverse side.

Talwin®
Brand of pentazocine (as lactate)
Analgesic for Parenteral Use

Ampuls: 30 mg. (1 ml.), **45 mg.** (1½ ml.), and **60 mg.** (2 ml.)
Vials: (10 ml.) 30 mg./ml.
30 mg. for I.V., I.M., or S.C. use
45 mg. for I.M. or S.C. use
60 mg. for I.M. or S.C. use

Indications: For the relief of moderate to severe pain. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindication: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.*

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. As with all strong analgesics, Talwin should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Tissue Damage at Injection Sites. Severe sclerosis of the skin, subcutaneous tissues, and underlying muscle have occurred at the injection sites of patients who have received multiple doses of pentazocine, as lactate. Constant rotation of injection sites is, therefore, recommended. In addition, animal studies have suggested that Talwin may be tolerated less well subcutaneously than intramuscularly.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Dermatologic Reactions: Soft tissue induration, nodules, and cutaneous depression can occur at injection sites. Ulceration (sloughing) and severe sclerosis of the skin and subcutaneous tissues (and, rarely, underlying muscle) have been reported after multiple doses.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *hematologic:* depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia; *other:* tachycardia, weakness or faintness, chills, allergic reactions including angioedema, edema of the face, vascular purpura, toxic epidermal necrolysis.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. When frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations:* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition. *Treatment:* Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

Talwin is not subject to narcotic controls.

How Supplied: *Uni-Amp® — Individual unit dose ampuls of 1 ml. (30 mg.) and 2 ml. (60 mg.)* in boxes of 25.

Ampuls of 1 ml. (30 mg.) in (nested) boxes of 25.

Ampuls of 1½ ml. (45 mg.) in boxes of 10 and 100.

Ampuls of 2 ml. (60 mg.) in (nested) boxes of 25.

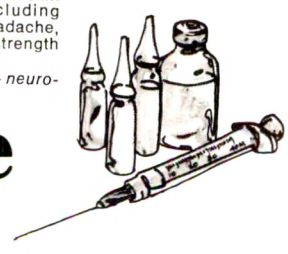
Each 1 ml. contains Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection.

Multiple dose vials of 10 ml., each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1. The pH of Talwin solution is adjusted between 4 and 5 with lactic acid and sodium hydroxide. The air in the ampuls and vials has been displaced by nitrogen gas.

Winthrop Laboratories, New York, N.Y. 10016

Winthrop

(1660M)



The alternative to opiates.

Injectable Talwin® Brand of pentazocine (as lactate)

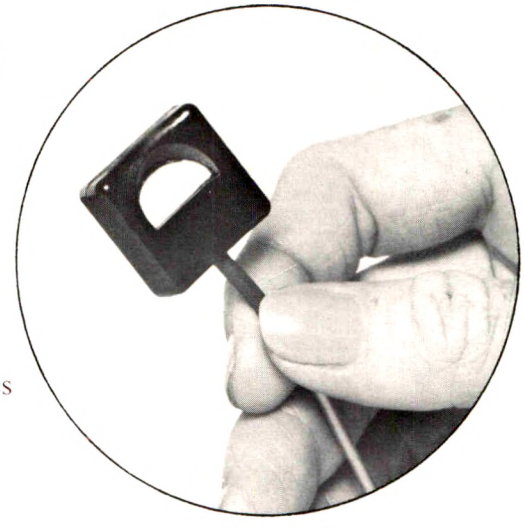
For monitoring Doppler sounds of blood flow and to take Doppler systolic blood pressure

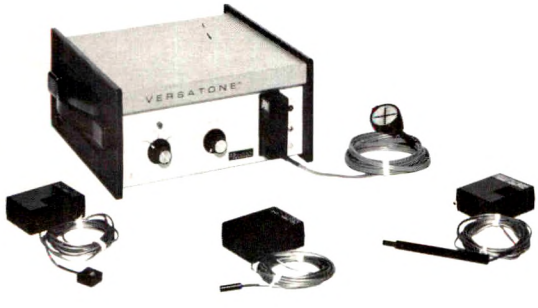
When used with a standard cuff and manometer

VERSATONE™

Multipurpose Doppler instrument with P84 probe

- Sensitive flat probe, easy to position and tape in place for continuous monitoring of the Doppler sounds of blood flow.
- Provides accurate non-invasive systolic pressures even on severely hypotensive patients.
- Optional sensor quiets the Doppler sound during electrocautery operation.
- Plug-in probe is readily interchangeable with other VERSATONE Doppler probes for detection of blood flow and venous air embolism.





Other VERSATONE probes

- Model P81
- Model P82
- Model P83

PLEASE CALL OR WRITE FOR FULL INFORMATION

MEDSONICS, INC.

790 HEMMETER LANE • P.O. BOX M, MOUNTAIN VIEW, CALIFORNIA 94042 • TELEPHONE (415) 965-3333

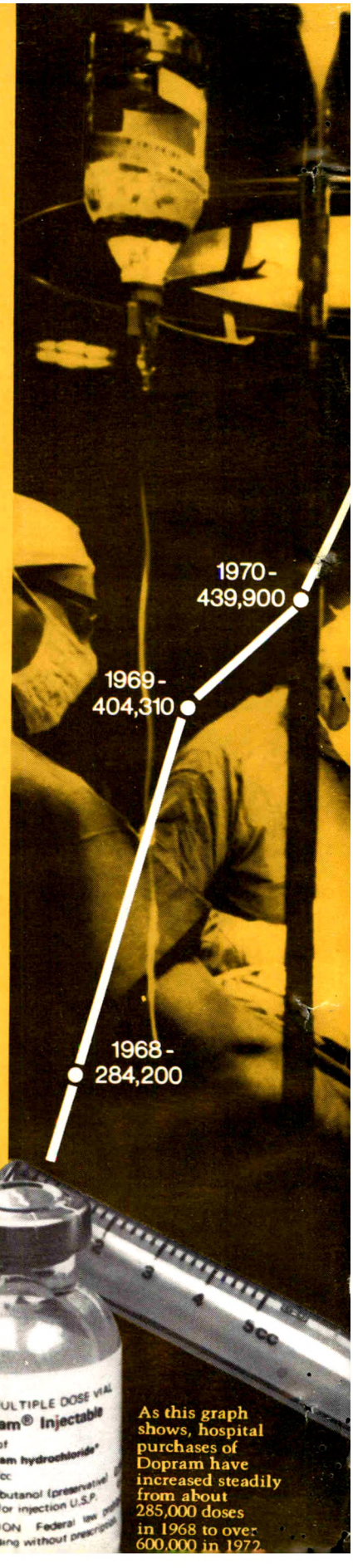
In all types of hospitals across the United States, its usage grows–

Dopram®
Injectable
(doxapram HCl)

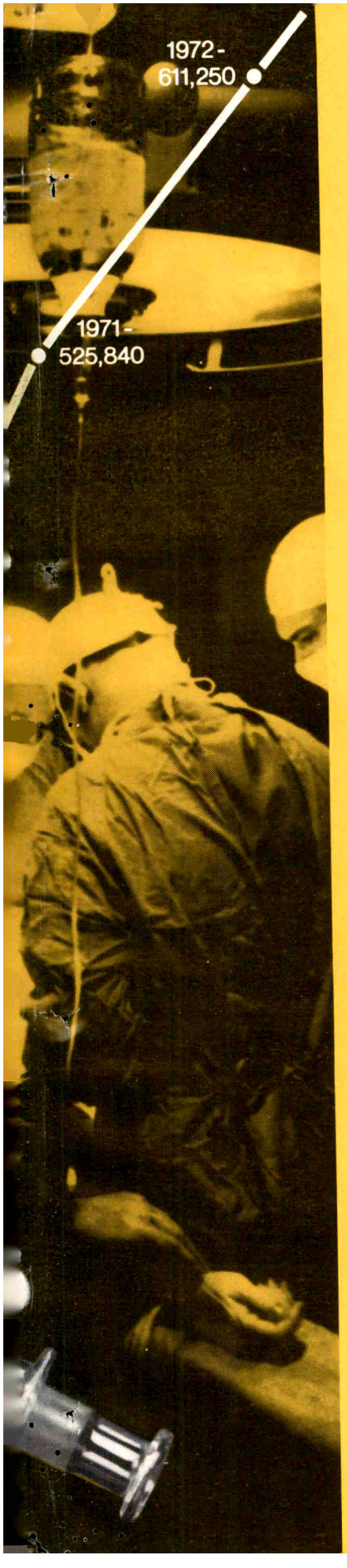
Seven years ago, A. H. Robins introduced Dopram, a unique respiratory stimulant developed in the company's research laboratories. What made this drug so useful to the anesthesiologist was its ability to rapidly restore the respiratory drive in patients with drug-induced post anesthetic depression.

Usage of Dopram has been steadily increasing each year, until today it has become a very important drug in the armamentarium of more than 1,500 hospitals of all types in all 50 states, the District of Columbia, and a number of foreign countries. These hospitals purchased more than 600,000 doses in 1972 alone.

Dopram–an important drug in anesthesiology. Try it for sighs!



As this graph shows, hospital purchases of Dopram have increased steadily from about 285,000 doses in 1968 to over 600,000 in 1972.



Indications

1. To stimulate respiration in patients with drug induced post-anesthetic respiratory depression or apnea other than that due to muscle relaxant drugs.
2. To pharmacologically stimulate deep breathing in the so-called "stir-up" regimen in the post-operative patient. Simultaneous administration of oxygen is desirable.
3. To hasten arousal and return of protective pharyngeal and laryngeal reflexes.
4. To aid in the differential diagnosis of post-anesthetic respiratory depression. Failure to adequately stimulate respiration suggests residual muscle relaxant effect.
5. To stimulate respiration, hasten arousal and to encourage the return of laryngopharyngeal reflexes in patients with mild to moderate respiratory and CNS depression due to drug overdosage.

Contraindications—Epilepsy and other convulsive states: incompetence of the ventilatory mechanism due to muscle paresis, flail chest, pneumothorax, airway obstruction, and extreme dyspnea; severe hypertension and cerebrovascular accidents; hypersensitivity.

Doxapram is not recommended for patients 12 years of age or under because studies to evaluate its safety and efficacy have not been performed.

Warnings—Doxapram is an analeptic agent; it is neither an antagonist to muscle relaxant drugs nor a specific narcotic antagonist. Since doxapram has an acid pH, it should not be mixed with alkaline solutions such as thiopental sodium.

Since narcosis may recur after stimulation with doxapram, care should be taken to maintain close observation until the patient has been fully alert for 1/2 to 1 hour. (Duration of drug 5-12 minutes.)

Doxapram is an adjunct to well-accepted supportive measures and resuscitative techniques. It may not stimulate adequate spontaneous breathing or provide sufficient arousal in patients who are severely depressed with CNS depressant drugs.

When doxapram is administered to postoperative patients or to patients in a state of narcosis with chronic pulmonary insufficiency, oxygen should be administered concomitantly. Failure to do so may result in further oxygen debt and more severe dyspnea due to the increased work of breathing.

Doxapram should be administered with great care and only under close supervision to patients with cerebral edema, bronchial asthma, severe tachycardia, cardiac arrhythmia, cardiac disease, hyperthyroidism and pheochromocytoma.

Usage in pregnancy

No adequate clinical studies have been performed to determine the safe use of doxapram in pregnancy. Until further clinical experience has been obtained, the physician must weigh the need against possible risks in using the drug in pregnant patients or in women of child-bearing potential.

Precautions—Recommended dosages of doxapram should be employed and maximum total dosages should not be exceeded. In patients with advanced pulmonary disease with hypoxemia, marked respiratory stimulation increases the work of breathing and may, thus, increase oxygen consumption and carbon dioxide production.

With excessive dosage, hyperventilation induced by doxapram may lead to respiratory alkalosis and hypocapnia with tetany and, theoretically, apnea.

An adequate airway is essential. In order to avoid side effects, it is advisable to use the minimum effective dosage. Monitoring of the blood pressure and deep tendon reflexes is recommended to prevent overdosage.

It is desirable that blood gases (P_{O_2} P_{CO_2} O_2 saturation) be monitored to assess the effectiveness of respiratory stimulation.

Intravenous barbiturates, oxygen and resuscitative equipment should be readily available to manage overdosage manifested by excessive central nervous system stimulation. Slow administration of the drug and careful observation of the patient during administration and for some time subsequently are advisable to insure possibility of post-stimulation respiratory depression must be kept in mind. In patients who have been lightly curarized, doxapram may temporarily mask the residual effects of muscle relaxant drugs.

Doxapram should be administered cautiously to patients receiving sympathomimetic or monoamine oxidase inhibiting drugs, since a synergistic pressor effect may occur. It should likewise be used with care in post-operative patients with marked dyspnea due to obstructive pulmonary emphysema, acute or chronic asthma, profound metabolic disorders, severe to moderately severe hypertension, increased cerebrospinal fluid pressure, head injury and acute agitation.

Since doxapram may stimulate basal gastric secretion, it should be used with care in patients with peptic ulcer disease and in patients undergoing gastric surgery.

Vascular extravasation or use of a single injection site over an extended period should be avoided since either may lead to thrombophlebitis.

Hypocapnia accompanying forced ventilation is a potent stimulus to cerebral vasoconstriction; it may be postulated that some element of risk may exist from reduced cerebral blood flow following prolonged and intensive hyperventilation.

Since an increase in epinephrine release has been noted with doxapram, it is recommended that initiation of therapy with this respiratory stimulant be delayed for at least 10 minutes following the discontinuance of anesthetics known to sensitize the myocardium to catecholamines, such as halothane and cyclopropane.

As with other intravenous preparations, all precautions should be taken during administration of doxapram to insure that injection is made directly into a suitable vein; extravasation, and inadvertent intra arterial injection should be avoided.

Adverse reactions—The following adverse reactions have been reported: *Central and Autonomic Nervous Systems.* Hyperactivit feeling of warmth, sweating, muscle tremor clonus, increased deep tendon reflexes, dizziness, muscle spasticity, pyrexia, confusion, paresthesia, pupillary dilatation pilomotor erection, headache, bilateral babinski, fasciculation and carpopedal spasm. A grand mal seizure occurred 95 minutes after drug administration in a known epileptic patient who was on anticonvulsant medication.

Respiratory. Cough, dyspnea, laryngospas bronchospasm and hiccough.

Cardiovascular. Hypertension, sinus tachycardia, bradycardia, extrasystoles, lower T-waves, premature ventricular contractions, irregular heart rhythm, tightness in chest. Although a mild to moderate increase in blood pressure is no infrequent, such an increase may occasionally be of concern in hypertensiv patients.

Gastrointestinal. Nausea and/or vomitin salivation, stimulation of lower bowel, sour taste.

Genitourinary. Urinary retention, stimulation of urinary bladder with spontaneous voiding.

Miscellaneous. Pruritus, thrombophlebit

Laboratory Determinations. A decrease in hemoglobin, hematocrit, or red blood cell count has been observed in postoperative patients. In the presence of pre-existing leukopenia, a further decrease in WBC w observed following anesthesia and treatment with doxapram hydrochloride Elevation of BUN and albuminuria have been observed.

In some of the cases cited above, the patients had received multiple drugs concomitantly, thus preventing an absolute judgment as to the role of doxapram in these reactions.

Dosage—For complete information concerning dosage and administration s package insert.

Supply—Dopram (doxapram hydrochloride) is available in 20 cc rubb stoppered vials containing 20 mg/cc, wi chlorobutanol 0.5% as the preservative.

A. H. Robins Company
Richmond, Virginia 23220

A·H·ROBIN

The AN·TROL™ Circle System Is Here

...and suddenly tidal volume has a new significance

The AN·TROL system is a complete circle providing a new standard of performance in anesthesia delivery. For the first time, a single system offers:

- A separation of tidal volume resulting in
  —preferential exhaust of alveolar gas
  —conservation of reusable patient dead space gas
- Full utilization of fresh gas—no waste
- Improved efficiencies regardless of rate of inflow
- Reduction of hazards of cross infection
- Adaptability to existing anesthesia machines

With the unique AN·TROL design, the exhaust of fresh and dead space gases is delayed until alveolar gas has been expelled. This engineered efficiency allows the AN·TROL circle to be used as a non-rebreathing system for the average adult patient at a moderate five liter inflow. At lower flows, efficiency is maintained by employing the AN·TROL in-line CO_2 absorber.

The convenient, single-use patient circle, the practical CO_2 absorber canister, the high quality, durable control arm—all combine to make the AN·TROL Anesthesia Circle System* the new symbol of excellence in anesthesia delivery.

For descriptive literature about the system or information about the AN·TROL free loan movie, write or call:

DIAMED
A DIVISION OF ILLINOIS TOOL WORKS INC.
830 LEE STREET / ELK GROVE VILLAGE, ILLINOIS 60007
TELEPHONE 312/593-8470

*patented or patent pending

Copyright 1975, Illinois Tool Works, Inc.

Now in your favorite color

This is your opportunity to color coordinate your OR. Dupaco is offering the color of your choice on any Ventura or Palomar anesthesia apparatus at no extra charge. It's a machine you have to work with all day long...wouldn't it be nice if it was finished in your favorite color. Dupaco's Ventura and Palomar anesthesia apparatus is designed to meet the most challenging requirements of the profession. Now is the time to put a little color in your life! Write for our apparatus catalog and we will return it with a color certificate that will entitle you to any single color of your choice, at no extra charge.

DUPACO
INCORPORATED

P.O. Box 98, San Marcos, CA 92069

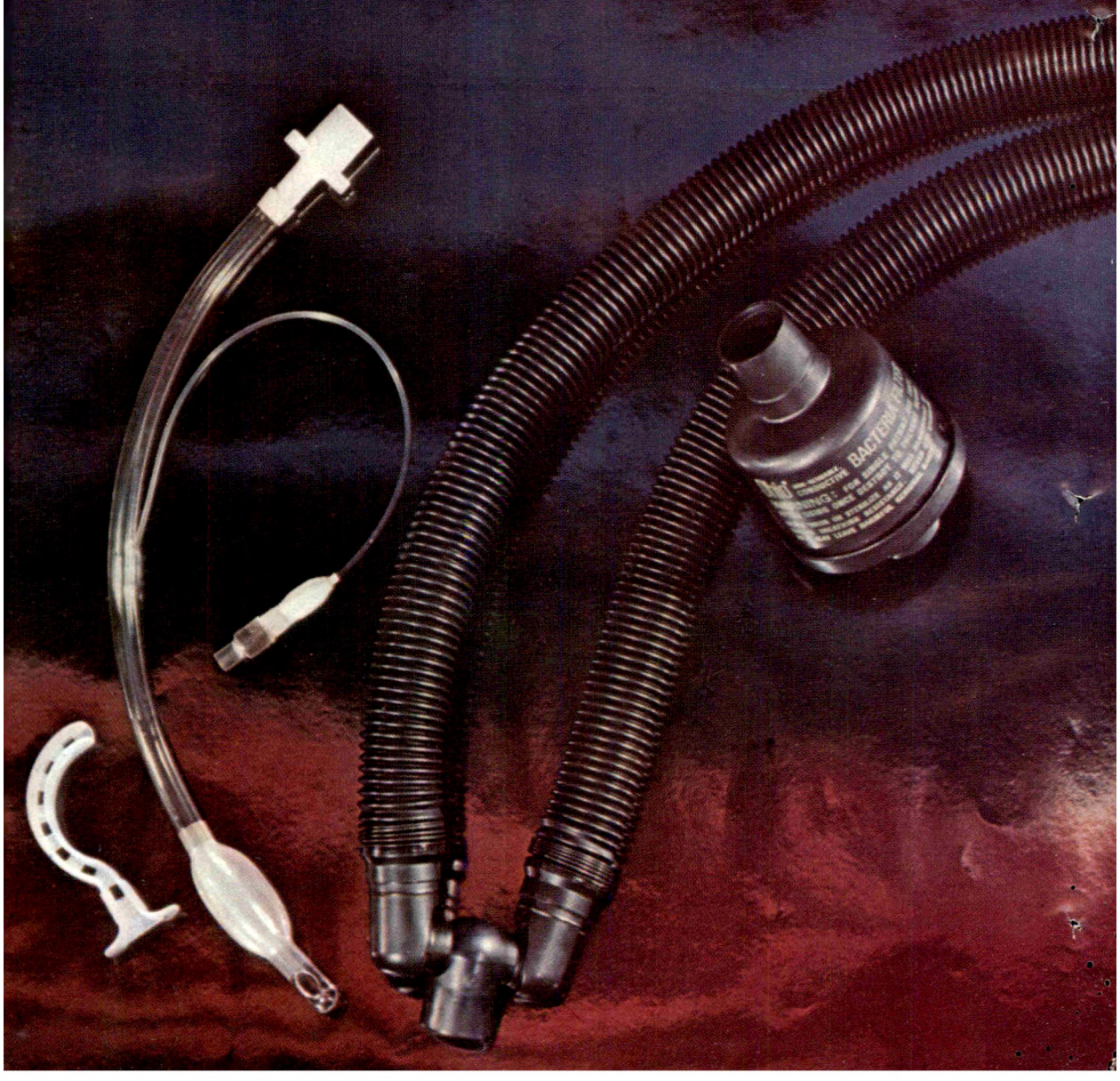
Effective Protection Against

OHIO® Disposable Conductive Anesthesia Breathing Circuit, with a bacteria filter so great we couldn't keep it to ourselves.

Nor would we want to. Because whether you're using our unique disposable filter as part of our circuit, or in someone else's (reusable or disposable), it's trapping and holding pathogens before they have an opportunity to reach your patient. Cutting chances of cross contamination.

And we think that's important.

In your sensitive hand, the latex bag enables you to "feel" the slightest ventilatory change. The integrated swivel "Y" is designed to accept a mask or endotracheal connection. Tubing is flexible, light and kink resistant.



Second-Hand Infection

OHIO offers three sizes in disposable, conductive, cushioned masks. Adjustable, so every facial contour can be fitted correctly and comfortably.

Also disposable airways, filters, suction valves, catheters and tubing. And the new, uncommon disposable endotracheal tubes, made by OHIO. With more ideas in design stage. So eventually your patients will get nothing second-hand.

Write for Catalog #1852. Or contact your OHIO representative about disposables. To make your operating room second to none in safety.

Ohio Medical Products AIRCO®
P.O. Box 1319, Dept. A&A
3030 Airco Drive
Madison, Wisconsin 53701

Uncommon disposables from the most commonly known name in anesthesia.

IMPORTANT INFORMATION ON THE 50th CONGRESS

Pre-registration Material, including program and hotel card—has been mailed to all I.A.R.S. members, educational members and associate members. Additional copies available on request from Cleveland business office.

Scientific Exhibit Space—Send requests for applications to I.A.R.S. Cleveland office promptly, since acceptance is subject to availability of space in exhibits section.

Technical (Commercial) Exhibit Space—Send requests for applications to: Charles B. Slack, Inc., Exhibit Manager, 6900 Grove Road, Thorofare, New Jersey 08086.

C.M.E. Credit—This Continuing Medical Education offering meets the criteria for 22 (est.) hours of credit in Category 1 for the Physician's Recognition Award of the American Medical Association.

International Anesthesia Research Society

50th CONGRESS

MARCH 14-18, 1976 CAESARS PALACE, LAS VEGAS, NEVADA

Propranolol and Surgical Anesthesia

JOEL A. KAPLAN, MD*
RONALD W. DUNBAR, MD†
Atlanta, Georgia‡

The potential danger of anesthetizing a patient on beta-adrenergic blockade therapy has long been recognized. The cases of 73 patients taking propranolol and anesthetized for noncardiac operations were reviewed with regard to preoperative administration of propranolol and intraoperative and postoperative complications. Of these patients, 72 percent took propranolol to within 24 hours of operation and 85 percent took it to within 48 hours. The mean dose of propranolol was 77 mg/day (range, 10 to 320 mg/day). Anesthetic techniques and agents included enflurane, halothane, N_2O-narcotic-relaxant, and spinal anesthesia. There were only three episodes of hypotension, all of which responded to a decreased depth of general anesthesia, IV fluid administration, and, in one patient, a small dose of a vasopressor. There were no intraoperative or postoperative deaths. It is concluded that if propranolol is indicated for medical control of the patient's symptoms, it need not be discontinued before surgical anesthesia.

PROPRANOLOL is an important drug in the medical management of patients with angina pectoris, hypertension, cardiac arrhythmias, thyrotoxicosis, pheochromocytoma, and obstructive cardiomyopathies.[1] An increasing number of patients can be expected to present for surgical anesthesia while taking this beta-adrenergic blocking agent.

Autonomic nervous system activity has been shown to be a major factor in maintaining circulatory integrity during anesthesia. Price and associates[2] reported a direct correlation between the depth of cyclopropane and ether anesthesia and plasma catecholamine levels. Sympathetic nervous system activity antagonizes the direct cardiovascular depression produced by general anesthetic agents such as cyclopropane, ether, fluroxene, and ketamine. There is also some evidence that sympathetic activity may be important with such other agents as halothane and morphine.[3,4]

The theoretic potential dangers of anesthesia in patients taking beta-adrenergic blocking agents have been reported since 1964.[5,6] The contention in these articles has been that beta-adrenergic blockade would result in profound myocardial depression during general anesthesia. However, there have been no reported studies of large groups of patients taking propranolol who have undergone anesthesia for noncardiac operations. The purpose of this study is to report our experience during 1 year with patients taking propranolol and coming for noncardiac surgical procedures.

METHODS

A series of 73 patients undergoing operations between January 1974 and January 1975 was reviewed for preoperative administration of propranolol and intraoperative or postoperative complications. Patients were analyzed as to age, dosage of and reason for taking propranolol, time between

*Assistant Professor of Anesthesiology, Director, Division of Cardiothoracic Anesthesia.
†Professor of Anesthesiology.
‡Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia 30322.

Paper received: 5/15/75
Accepted for publication: 6/2/75

discontinuing propranolol and induction of anesthesia, type of surgical procedure, anesthetic agents, and complications.

Patients were divided into four groups, according to how long their propranolol had been discontinued before induction of anesthesia:

Group I, <12 hours

Group II, 12 to 24 hours

Group III, 24 to 48 hours

Group IV, >48 hours

All complications were recorded during the anesthetic procedure, in the recovery room, and postoperatively. Hypotension was defined as a systolic blood pressure 20 percent below the lowest recorded preoperative blood pressure, and significant bradycardia was considered below 50 beats/min. Arrhythmias recorded were those occurring during the operative procedure.

Anesthetic technics included general, spinal, and local anesthesia with IV sedation. Of the patients who received general anesthesia, 90 percent were induced with thiopental (2 to 4 mg/kg IV), while 10 percent were induced with the inhalation agent itself. Anesthesia was maintained with 50 to 60 percent N_2O, and either halothane, enflurane, or narcotics and relaxants. Tetracaine 1.0 percent was used for all spinals. Lidocaine was administered for the two procedures under local anesthesia; both these patients were sedated with diazepam.

RESULTS

Seventy-two percent of the patients took propranolol within 24 hours of operation and 85 percent took it within 48 hours (table 1). The mean dose of propranolol was 77 mg/day (range, 10 to 320 mg/day). The larger doses were taken by those patients who continued the drug closest to operation. Most patients in groups III and IV were taking less than 80 mg/day, while most in groups I and II were taking 80 to 160 mg/day (fig 1). Only 2 percent of the group-I patients were taking over 160 mg/day.

TABLE 1
Patient Groups

Group	Number of patients	Hours off propranolol	Daily dose of propranolol, mg	
			Mean	Range
I	28	<12	90	20-320
II	25	12-24	81	10-160
III	9	24-48	72	20-160
IV	11	>48	44	20-160
Total	73		77	10-320

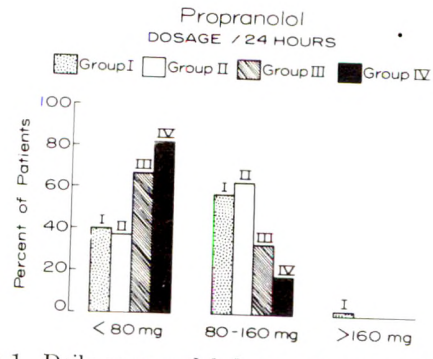


FIG 1. Daily propranolol dosage of groups I-IV. The larger doses (> 80 mg) were taken more often by those patients who received the drug closest to operation (groups I and II).

TABLE 2
Indications for Propranolol
(Number of Patients)

Group	Angina pectoris	Arrhythmias	Hypertension	Hyperthyroidism
I	12	9	6	1
II	13	8	4	
III	4	3	2	
IV	2	6	3	
Total	31	26	15	1

Most patients (77 percent) were receiving propranolol for the treatment of either angina pectoris or cardiac arrhythmias (table 2). Propranolol was taken by 20 percent for control of hypertension, and 1 patient was being treated for hyperthyroidism.

All types of surgical procedures were included except cardiac (table 3).

Enflurane was the most frequently used anesthetic agent (fig 2), followed in order by balanced N_2O-narcotic-relaxant, halothane, spinal, and local. Local anesthesia with sedation was used only in 2 patients in group I. In this series, no cyclopropane, ether, or fluroxene was used, since these are flammable.

The three episodes of hypotension (table 4) involved 1 patient each in groups I, II, and IV; all responded to decreasing the

TABLE 3
Type of Surgical Procedures
(Number of Patients)

Type of surgery	I	II	III	IV	Total
Upper abdominal	4	6	3	3	16
Perineal	4	5	4	1	14
Vascular	8	2	—	1	11
Chest wall	—	4	2	2	8
Peripheral	4	3	—	—	7
Lower abdominal	4	—	—	2	6
Neck	4	—	—	2	6
Neurosurgery	—	3	—	—	3
Thoracic	—	2	—	—	2

TABLE 4
Complications

Group	Number of patients	Hypotension	Bradycardia	Arrhythmia	Postoperative myocardial infarction
I	28	1	—	—	—
II	25	1	1	—	1
III	9	—	—	1	—
IV	11	1	—	1	—
Total	73	3	1	2	1

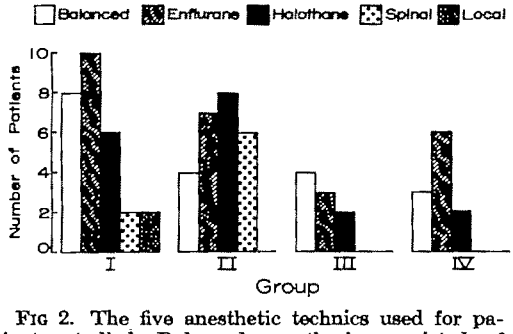


FIG 2. The five anesthetic technics used for patients studied. Balanced anesthesia consisted of N_2O, narcotic, and muscle relaxant. Enflurane was the most commonly used anesthetic agent.

depth of general anesthesia, IV fluid administration, and a small dose of vasopressor in one. Two of these patients were taking between 80 to 160 mg/day of propranolol and one was taking less than 80 mg/day. Two were anesthetized with a balanced anesthetic technic consisting of N_2O, morphine, and pancuronium; enflurane-N_2O was used for the other. Two other patients developed nodal rhythms during enflurane anesthesia; in one case, this was converted to a regular sinus rhythm by 0.4 mg of atropine.

One patient showed a subendocardial myocardial infarct on a postoperative ECG. He had been taking 160 mg/day of propranolol for angina pectoris until 18 hours before operation and had had a myocardial infarct 2 years previously. This patient, 64 years old and weighing 80 kg, had been premedicated with 5 mg of morphine, 10 mg of diazepam, and 0.4 mg of atropine IM 1 hour before arriving in the operating room. Upon arrival, his heart rate was 48 beats/min, increasing to 60 beats/min after 0.4 mg of atropine IV. He had an otherwise uneventful general anesthesia with a thiopental induction and maintenance with enflurane-N_2O. His postoperative course was smooth, and he was discharged in satisfactory condition.

There were no intraoperative or postoperative deaths in this series.

DISCUSSION

When the potential dangers of general anesthesia and antihypertensive agents were first reported in 1955, it was recommended that these agents be discontinued 2 weeks before operation.[7] Since then, studies by Ominsky and Wollman[8] and by Prys-Roberts and coworkers[9] have clearly shown that hypertensive patients should be continued on their therapy until the time of operation.

Patients taking propranolol are in an analogous situation. If the patients require the drug for the control of their disease, they may safely be continued on it until within 12 hours of (noncardiac) operation, as this study demonstrates.

In 1964, Craythorne and Huffington[10] reported that propranolol administered to dogs anesthetized with halothane produced minimal cardiovascular effects. The only significant change was a decrease in heart rate. Other studies in dogs and patients have shown that IV administration of beta-blocking agents can lead to hypotension and decreased cardiac output.[11-18] However, in all these studies, the beta-blocking agent has been given IV during general anesthesia. The anesthesiologist giving an anesthetic to a patient on chronic (oral) propranolol therapy is in a somewhat different situation. Here, the anesthetic agent can be carefully

administered to the patient, who has a fixed level of beta-blockade. We believe that this is a significant difference and may account for our good results.

The only major complications attributed to preoperative propranolol administration were in 5 patients reported by Viljoen's group,[14] in whom difficulty was encountered in discontinuing cardiopulmonary bypass after coronary artery surgery. These patients had complex operations involving internal mammary artery implantation and a ventricular aneurysmectomy. All these patients had postoperative left ventricular failure, attributed to their propranolol intake. However, other factors, including inadequate revascularization of the myocardium due to the internal mammary artery implant (Vineberg procedure), poor left ventricular function, and myocardial depression secondary to methoxyflurane, may have caused the low output states. On the basis of this small group, Viljoen recommended withdrawal of propranolol for 2 weeks before cardiac surgery. Others have generalized this to suggest withdrawal of propranolol 2 weeks before *all* operations.

Recently, we[15] reported a series of 169 consecutive patients undergoing cardiac operations. Of these, 82 percent had received propranolol to within 2 weeks of operation, and 52 percent received the drug to within 48 hours of operation. The incidence of hypotension and bradycardia was found to be no different in the patients taking propranolol than in those not taking the drug. Two other studies, by Caralps and colleagues[16] and by Moran's group,[17] support our findings.

If propranolol is to be discontinued preoperatively, the dose should be slowly tapered, not abruptly stopped, as sudden withdrawal can lead to myocardial infarction in the patient with ischemic heart disease.[18,19] We believe the 1 patient in group II whose ECG showed a subendocardial myocardial infarct postoperatively may have sustained the infarction preoperatively after discontinuing propranolol. This would account for his significant bradycardia upon arrival in the operating room. Fortunately, he tolerated the general anesthetic quite well.

Evans and Shand[20] have shown the half-life of propranolol to be 3.4 to 6 hours after discontinuing chronic administration in normal man. Faulkner and associates[21] reported that propranolol disappears from the plasma and atrium in 24 to 48 hours. Studies by Faulkner[21] and by Kaplan[15] of myocardial contractility, using systolic time intervals, have shown that the preejection period and the preejection period/left ventricular ejection time (PEP/LVET) intervals return to normal 24 to 48 hours after discontinuing the drug.

However, since propranolol decreases myocardial contractility, cardiac output, and heart rate, the anesthesiologist must understand the pharmacology of beta-adrenergic blockade and its treatment, if patients are to be continued on the drug until operation. Hypotension during anesthesia should be treated by decreasing the depth of general anesthesia, increasing IV fluid administration, altering surgical manipulation and position of the patient, and administering vasopressors such as ephedrine, as required. For bradycardia, atropine should be given to reduce vagal tone.

In the unlikely event that these steps do not reverse the situation and it is felt that the beta-blockade is contributing to the condition, specific treatment of the beta-blockade should be undertaken (fig 3). An isoproterenol drip can be used to directly compete for the beta receptor; however, larger doses than usual will be required. In cardiac patients, we have used doses in the range of 5 to 20 μg/min. Glucagon has a separate receptor site on the cell wall and releases adenyl cyclase to produce cyclic-AMP independent of the beta-receptor.[22] We have used 5 to 10 mg as an IV bolus, followed by a 1 mg/min via IV drip. Finally, $CaCl_2$ and digitalis work intracellularly at the level of the contractile proteins to improve myocardial contractility;[23] 250 to 1000 mg of $CaCl_2$ given slowly IV will effectively bypass beta-adrenergic blockade.

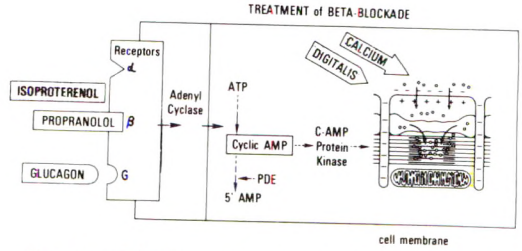


FIG 3. Diagrammatic representation of beta-adrenergic receptor blockade and its treatment. The block can be competitively antagonized with isoproterenol or bypassed with glucagon, calcium, or digitalis.

CONCLUSIONS

Patients requiring propranolol to within 24 to 48 hours of noncardiac operations can be safely anesthetized. Therefore, should the drug be determined to be necessary for medical control of the patient's symptoms, it should not be discontinued many days before surgery. However, as in all anesthetic procedures, the anesthesiologist should have a thorough knowledge of the pharmacology of all drugs taken by his patient and be prepared to cope with any untoward response.

REFERENCES

1. Merin RG: Anesthetic management problems posed by therapeutic advances: III. Beta-adrenergic blocking drugs. Anesth & Analg 51:617-624, 1972

2. Price HL, Linde HW, Jones RE, et al: Sympathoadrenal responses to general anesthesia in man and their relation to hemodynamics. Anesthesiology 20:563-575, 1959

3. Price HL, Skovsted P, Pauca AL, et al: Evidence for beta-receptor activation produced by halothane in normal man. Anesthesiology 32:389-395, 1970

4. Hasbrouck JD: Morphine anesthesia for open heart surgery. Ann Thorac Surg 10:364-368, 1970

5. Johnstone M: Beta-adrenergic blockade with pronethalol during anaesthesia. Br J Anaesth 36: 224-232, 1964

6. Johnstone M: Propranolol during halothane anaesthesia. Br J Anaesth 38:516-529, 1966

7. Foster MW, Gayle RF: Dangers in combining reserpine with electroconvulsive therapy. JAMA 159:1520-1522, 1955

8. Ominsky AJ, Wollman H: Hazards of general anesthesia in the reserpinized patient. Anesthesiology 30:443-446, 1969

9. Prys-Roberts C, Meloche R, Foex P: Studies of anesthesia in relation to hypertension. I: Cardiovascular responses of treated and untreated patients. Br J Anaesth 43:122-136, 1971

10. Craythorne NWB, Huffington PE: Effects of propranolol on the cardiovascular response to cyclopropane and halothane. Anesthesiology 27:580-583, 1966

11. Weis KH, Brackenbusch R: On the cardiovascular effect of propranolol during halothane anaesthesia in normovolemic and hypovolemic dogs. Br J Anaesth 42:272-278, 1970

12. Jorfeldt L, Lofström B, Moller J, et al: Cardiovascular effects of beta receptor blocking drugs during halothane anaesthesia in man. Acta Anaesthesiol Scand 14:35-44, 1970

13. Stephen GW, Davie IT, Scott DB: Hemodynamic effects of beta receptor blocking drugs during nitrous oxide and halothane anaesthesia. Br J Anaesth 43:320-324, 1971

14. Viljoen JF, Estafanous FG, Kellner GA: Propranolol and cardiac surgery. J Thorac Cardiovasc Surg 64:826-830, 1972

15. Kaplan JA, Dunbar RW, Bland JW, et al: Propranolol and cardiac surgery: a problem for the anesthesiologist? Anesth & Analg 54:571-578, 1975

16. Caralps JM, Mulet J, Wienke HR, et al: Results of coronary artery surgery in patients receiving propranolol. J Thorac Cardiovasc Surg 67:526-529, 1974

17. Moran JM, Mulet J, Caralps JM, et al: Coronary revascularization in patients receiving propranolol. Circulation 49-50 (suppl II):II-116, 1974

18. Nellem M: Withdrawal of propranolol and myocardial infarction. Lancet 1:558, 1973

19. Diaz RG, Sonberg J, Freeman E, et al: Myocardial infarction after propranolol withdrawal. Amer Heart J 88:257-258, 1974

20. Evans GH, Shand DG: The disposition of propranolol. VI. Independent variations in steady-state circulating drug concentrations and half-life as a result of plasma binding in man. Clin Pharmacol Ther 14:494-500, 1973

21. Faulkner SL, Hopkins JT, Boerth LC, et al: Time required for complete recovery from chronic propranolol therapy. N Engl J Med 289:607-609, 1973

22. Glick G, Parmley WW, Wechsler AS, et al: Glucagon: its enhancement of cardiac performance in the cat and dog and persistence of its inotropic action despite beta receptor blockade with propranolol. Circ Res 22:789-799, 1968

23. Denlinger JK, Kaplan JA, Lecky JH, et al: Cardiovascular responses to calcium administered intravenously to man during halothane anesthesia. Anesthesiology 42:390-397, 1975

Visual Communication: Clarity in Lecture Slides Revisited

STANLEY J. McCOMB
Rochester, Minnesota

DESPITE the numerous articles related to the lack of legibility of lantern slides shown at medical and scientific meetings and to the definite need for improvement in this vital area of visual communication there continues an amazing, almost callous disregard of some of the fundamental requirements for the production of satisfactory lecture slides. That visual communication suffers is obvious from such a statement as, "It wasn't the first time I'd seen a gathering of insects palmed off as a collection of data."[1] Or as Fuller[2] reported, of fifty-two speakers before various sectional meetings of the AAAS, twenty-three apologized for their slides.

That deficient visual communication is an all too common fault in slides is implied by the efforts of various national medical and scientific societies to acquaint their speakers with the basic requirements for making satisfactory slides to be shown at their meetings. The American College of Physicians sends its speakers specific recommendations concerning the organization and limitation of data on a slide. The Ethyl Corporation has furnished a pamphlet, *Make Slides Worthwhile*. The American College of Chest Physicians has supplied its speakers with a slide format or template, with typing and spacing suggestions. And it is significant that, in a more wide-ranging field, the magazine *Successful Meetings* recently has added an audiovisual consultant to its staff. This certainly offers evidence that there exists a widespread disregard of available information and means for achieving effective visual communication in lecture slides and that the lack of application of some of the basics in this connection lies almost uniformly with the author. It is to this group that this paper is addressed.

The need for communication is universal. Practically everyone has seen reproductions

FIG 1. American Indian visual. (From Christensen EO: Primitive Art. New York, Thomas Y. Crowell Company, 1955, p 337. By permission of The Studio Publication, Inc.)

of drawings made by primitive peoples to communicate events and ideas, from cave paintings in various parts of the world to the products of our own Indians (fig 1); and one is impressed that their effectiveness is due in large part to directness and simplicity that lead to practically instant interpretation. Now it might justifiably be said that today there is so much more to communicate—but herein lies the challenge: the need for careful evaluation of what needs to be communicated and how best to transfer it to the screen. Despite broad acknowledgment of the effectiveness of slides in communication, it is a fact that they remain an abused, sometimes overused adjunct to a verbal presentation.

Emeritus Head of Section of Photography, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Before analysis of their faults, slides should be divided into their main categories. The most common undoubtedly is the statistical or data slide, sometimes called "tabular." Chart and graph slides make up another large group; and then there are slides that may be referred to as "pictorials." This paper will deal primarily with data, chart, and graph slides.

Certainly the foremost complaint is illegibility due to crowding—simply, the incorporating of too much data (fig 2). Kern[3] has said: "Don't put too many data on a single slide, especially irrelevant data. . . . This unhappy mistake is the one most frequently committed: the author is too lazy to construct a brief summary of salient data, so he presents instead a detailed table that will occupy a full page in the printed paper." Other factors affecting legibility are improper letter size in relation to screen-image size and poor organization. Obviously all these are interrelated. Charts may be ineffective because of poor design or layout and—if done in color—because of unsatisfactory color combinations and contrast.

Another major fault is use of material prepared initially as an illustration for publication (fig. 3). This may be quite inappropriate for a slide presentation. In published form such data may be referred to repeatedly for correlation with the text, but a slide usually cannot be given more than a quick one-time appraisal. The average viewer can absorb, understand, and retain just so much data in normal viewing time per slide. What the viewer requires, deserves, and expects is a succinct summary of the material presented verbally, not the step-by-step documentation of investigation. Audy[4] has stated it well: "Slides have three functions: 1, to support the spoken word; 2, to amplify the spoken word; 3, to replace the spoken word." That is, "Some things are much better conveyed by a diagram or chart than by description. . . ." And most certainly, a slide is not intended as a teleprompter!

FIG 2. ". . . and this slide clearly explains the principle underlying this very important concept. Next slide, please. . . ." (Courtesy of Barry Baker, Art Director, Baylor College of Medicine; Audy JR: Delivery of papers at scientific meetings. J Biocommun 1:30-33 [Nov], 1974. By Permission of The Association of Medical Illustrators and The Health Sciences Communications Association.)

LATE POSTOPERATIVE COMPLICATIONS

Complication	Frequency (N = 30) 1942-1968 No. (%)	(N = 24) 1969-1973 No. (%)	(N = 54) 1942-1973 No. (%)
Pain	13 (43)	10 (42)	23 (43)
Weight loss	13 (43)	8 (33)	21 (39)
Steatorrhea	9 (30)	6 (25)	15 (28)
Insulin shock	9 (30)	5 (21)	14 (26)
Frequent insulin reactions	6 (20)	5 (21)	11 (20)
Jaundice	6 (20)	4 (17)	10 (18)
Diabetic ketoacidosis	5 (17)	2 (8)	7 (13)
GI bleeding	6 (20)	0 (0)	6 (11)
Dumping syndrome	3 (10)	1 (5)	4 (7)
Diabetic neuropathy	4 (13)	0 (0)	4 (7)
Urinary-tract infection	2 (7)	2 (8)	4 (7)
Edema	2 (7)	2 (8)	4 (7)
Strictured biliary anastomosis	3 (10)	1 (5)	4 (7)
Biliary-tract stones	3 (10)	0 (0)	3 (6)
Cirrhosis	3 (10)	0 (0)	3 (6)
Phlebitis	3 (10)	0 (0)	3 (6)
Intra-abdominal abscess	1 (3)	1 (5)	2 (4)
Nephrolithiasis	2 (7)	0 (0)	2 (4)
Diabetic retinopathy	2 (7)	0 (0)	2 (4)
Psychosis	2 (7)	0 (0)	2 (4)
Angina pectoris	2 (7)	0 (0)	2 (4)
Perforated peptic ulcer	2 (7)	0 (0)	2 (4)
Pleural effusion	0 (0)	2 (8)	2 (4)
Anemia	1 (3)	1 (5)	2 (4)
Spontaneous intraperitoneal hemorrhage	2 (7)	0 (0)	2 (4)
Other	7 (23)	4 (17)	11 (20)
Total	111	54	165
Complications per patient	3.7	2.3	3.1

FIG 3. Mass of data satisfactory for publication but worthless as a slide.

As overcrowding of slides with needless data is criticized by all authors dealing with improvement in lecture slides, what remedies are available? One is condensation and better organization of data. At the Mayo Clinic, Hewitt, striving long ago to improve tabular slides, prepared exhibits demonstrating possibilities inherent in organization and classification of data. "Slides are not essays. You will be present to amplify. . . . Condensation requires deletion of detail." He suggested methods for improvement: restrict data to major points; condense text; classify and isolate (fig 4); and wherever possible, present data in graph form.

When a great volume of data is considered absolutely essential, consideration must be given to reorganization; and if effective consolidation is not possible, the data should be presented in additional sequential slides (fig 5). As to reorganization, one author posed the question of WILL/WON'T, which should be applied to every visual. WILL this image help to make my point? WON'T the

43-YEAR-OLD HOUSEWIFE

Admitted to Mayo Clinic 1 Aug 73

CC: low back pain of 15 years' duration. While at clinic routine chest x-ray revealed 3-cm solitary nodule in RLL with definite calcification.
On 24 Aug 73 R thoracotomy because of suspected bronchogenic carcinoma. Lesion was granuloma; histologic diagnosis histoplasmosis, positive for Cryptococcus neoformans.
PH: dry cough for many years. Physical exam of chest neg. No evidence that back pain could be related. Spinal tap not done.

A

43-YEAR-OLD HOUSEWIFE

Admitted MC 1 Aug 73
CC: Low back pain for 15 yr
PH: Dry cough many yr
Chest Px neg; no spinal tap
No evidence cough related to back pain
Ex: Chest x-ray—solitary 3-cm nodule with definite calcification in RLL (Bronchogenic ca suspected)
R thoracotomy 24 Aug 73
Granuloma; histologic Dx histoplasmosis, culture pos for C. neoformans

B

FIG 4. Running text (*A*) needs reorganization (*B*) for more rapid interpretation.

presentation be just as clear without it? This calls for a ruthless assessment of data to avoid possible application (fig 6) of the doggerel of Hewitt:

> His audience yawned, it squirmed and it sighed;
>
> He constantly put too much on a slide.

These general problems impose a need of more specific methods and techniques for their solution. As in many other endeavors, it is best to establish some ground rules before proceeding. The predominant slide form today is the 50-mm size (2 by 2 inches) using 35-mm film in a mask opening of 3:2 ratio (34 by 23 mm) oriented horizontally. Although the 2 by 2 slide can be used in a vertical orientation, this is not recommended, for there is very real risk in some situations of having part of the image extend beyond the upper or lower limit of the screen.

Within the frame described, what will be legible? There are well-established criteria for this. One is derived from the Snellen Test Chart for measuring visual acuity. In effect, for a letter to be just legible the entire letter must subtend an angle of 0° 5′ at the viewer's eye. For example, to subtend

HYPERTENSION EMERGENCIES
Sodium Nitroprusside
Now available as "Nipride" (Roche)
Use: 50 mg per 500 to 1000 ml. of 5% dextrose in water. Cover with aluminum foil. Use only 4 hours. Give i.v. by perfusion pump or micro-drip regulator.
Actions: Direct-acting vasodilator.
Decreases BP within seconds
Decreases PVR
Decreases CO (capitance pooling)
No change in GFR or ERPF
Effects stop within seconds; BP back to pretreatment levels in 1 to 10 min.
Side-Effects: Those of lowering BP too rapidly: Nausea, headache, restlessness, muscle twitching, palpitation.
Thiocyanate is end metabolic product (less than 10 mg/dl is safe concentration during prolonged administration.) One case of hypothyroidism.

A

HYPERTENSION EMERGENCIES
Sodium Nitroprusside
Now available as "Nipride" (Roche)
Use: 50 mg per 500 to 1000 ml. of 5% dextrose in water. Cover with aluminum foil. Use only 4 hours. Give i.v. by perfusion pump or micro-drip regulator.

B

HYPERTENSION EMERGENCIES
Sodium Nitroprusside (Continued)
Actions: Direct-acting vasodilator.
Decreases BP within seconds
Decreases PVR
Decreases CO (capitance pooling)
No change in GFR or ERPF
Effects stop within seconds; BP back to pretreatment levels in 1 to 10 min.

C

HYPERTENSION EMERGENCIES
Sodium Nitroprusside (Continued)
Side-Effects: Those of lowering BP too rapidly: Nausea, headache, restlessness, muscle twitching, palpitation.
Thiocyanate is end metabolic product (less than 10 mg/dl is safe concentration during prolonged administration.) One case of hypothyroidism.

D

FIG 5. Information too tightly packed in one slide (*A*) is more readily grasped when presented in more (*B, C, D*), because then it can be seen.

an angle of 5′ at the pupil of a viewer 100 feet from the screen, a letter on the screen must be 37 mm (1½ inches) high. A more easily grasped rule, applicable to any size conference room, requires that the maximum viewing distance not exceed six times the

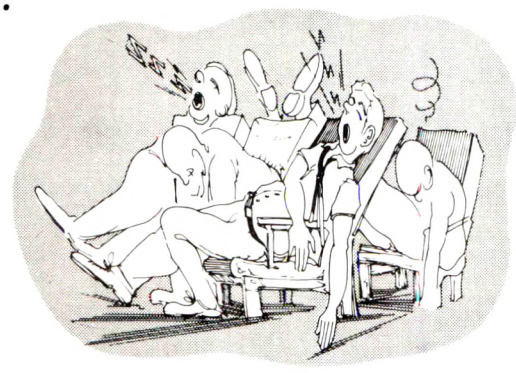


FIG 6. "He constantly put too much on a slide." (Courtesy of John W. Desley, Medical Graphics, Mayo Clinic and Mayo Foundation.)

width of the whole-slide image on the screen. This relation is based on the Room Image Factor (RIF), developed by Maurer from earlier studies by Gage on the optimum projected image size in relation to room length. While this ratio of six times screen width may appear to be conservative, it must be remembered that the viewer for whom it is intended is the one farthest from the screen.

As an aid in achieving greater legibility in slides, use of a standard format for original copy is suggested. Since copy for most tabular slides is prepared on a typewriter, a standard format may be used without difficulty. The format suggested provides for an information area 113 by 75 mm (4½ x 3 inches), and once this area has been determined it may be developed in multiples on a sheet of good quality paper of letter size (fig 7).

Text should be limited to nine double-spaced lines, each line containing no more than 54 total spaces if in elite type or 45 for pica.

Copy prepared in this fashion assures legibility for practically all viewing situations. Characters should be firm and black throughout. Available are special carbon paper ribbons (one-time use only) that yield superior copy. A new—emphasis on *new*—cloth ribbon is an alternative, for which one author adds a suggestion to reverse carbon paper so that the imprint is repeated on the back of the typed copy. Simply, the blacker the copy the better will be the slide.

Turning now to charts and graphs (which may be termed "art work" by some, or "graphics"), all the recommendations offered above for improved legibility apply again—organization of data, restriction to absolute essentials, simplification, and appropriate size and style of letters and numerals for the copy to be photographed. In preparing this type of material, many graphic artists use 229 by 152 mm (9 by 6 inches), again horizontally, as the maximum information area. Using this standard format resolves many problems related to layout,

SUGGESTED TYPING TEMPLATE

Double space all lines.

FIG 7. Template for typing copy.

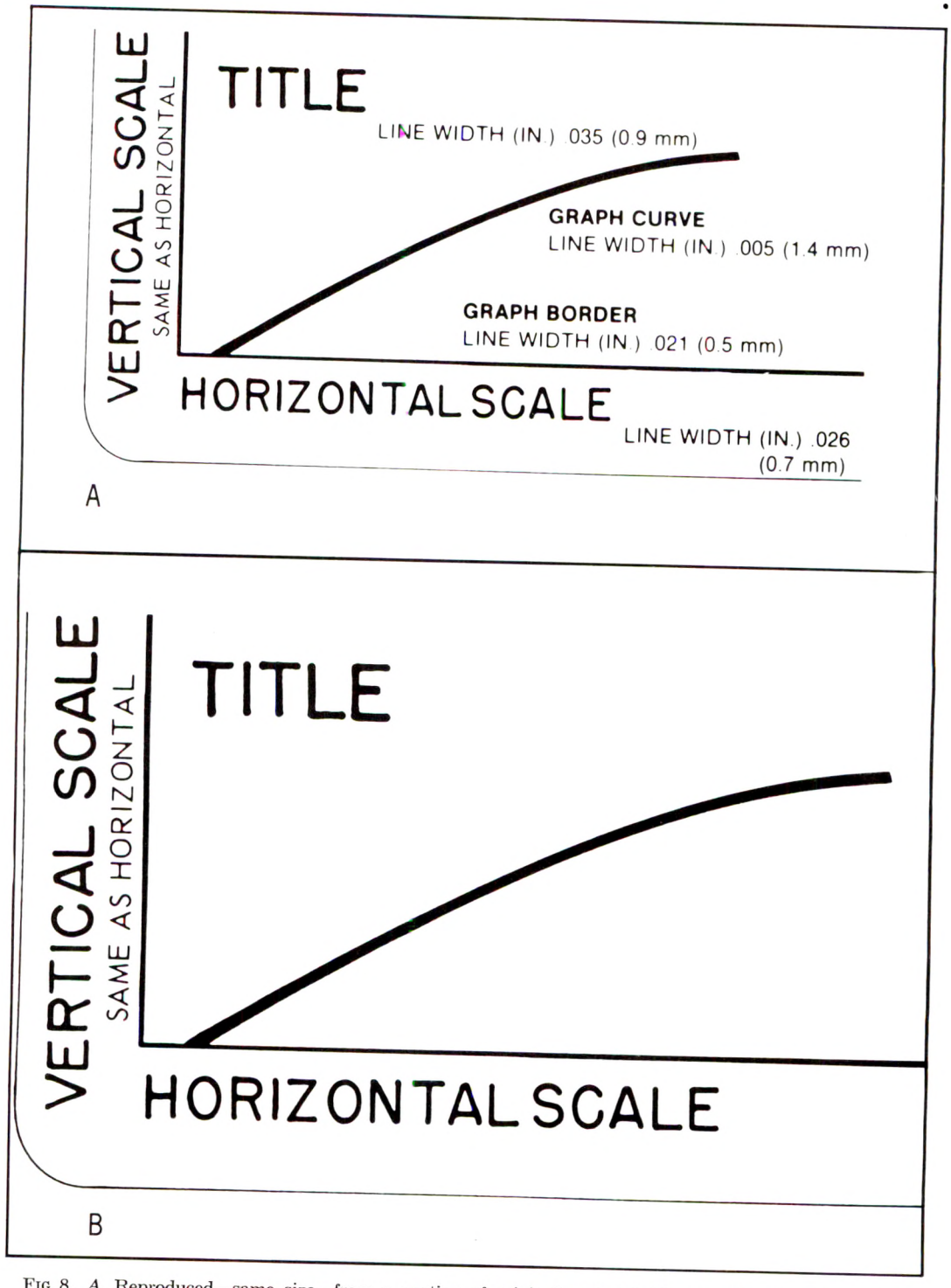


FIG 8. *A*, Reproduced—same size—from a portion of original material 152 mm wide by 101 mm high (6 by 4 inches) with appropriate line and letter widths. Compare with *B*, for original 229 mm wide by 152 mm high (9 by 6 inches), for which letter and line widths must be one-third greater than in *A*. For example: graph curve line width of 1.4 mm becomes 1.8 mm.

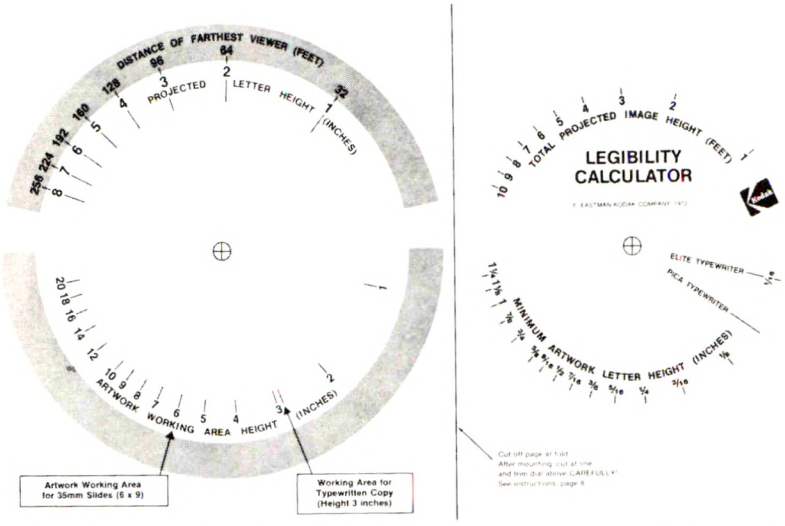


FIG 9. Legibility Calculator. (Reproduced from Kodak Pamphlet S-24: Legibility—Art Work to Screen. Rochester, New York, Motion Picture and Audiovisual Markets Division, Eastman Kodak Company.)

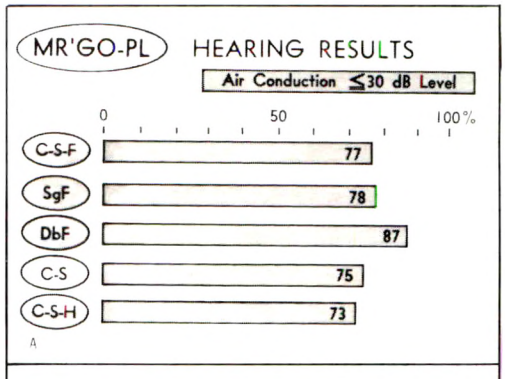
letter height, and line weight (thickness), right on down to the photographic aspects.

From the legibility criteria presented earlier it has been determined that letter height should not be less than 1/25 of the specified copy/image width. It applies to both situations, which means that an "office situation" check of legibility may easily be made. Usually, six times the width of copy would require viewing at about arm's length for typed slides and about double that for charts. The Eastman Kodak Company provides a legibility guide for letter height and line weight for main titles and subheadings (fig 8) and a legibility calculator for quick reference (fig 9).

Information usually is grasped more readily in graph form than in tabular form, and that is what visual communication is all about—comprehension and understanding. Bar graphs (fig 10) and pie charts (fig 11) are particularly effective for comparisons of data. These may be prepared easily from a variety of graphic aids such as pressure-sensitive tapes available in a variety of widths and colors, patterned adhesive overlays, and letters. In this way it is possible to create slides that are more readily perceived.

There does exist some justifiable criticism of the customary black letters on a white background slide, with resultant glare from the large expanse of white. Even so, it is preferable to the "reverse text" slide (white on black). The latter does have an advantage in that the words and numbers, being transparent, can be colored by application of water colors, dyes, or transparent tapes.

A very satisfactory solution to the glare problem is to introduce color in the background. This may be done by photographing

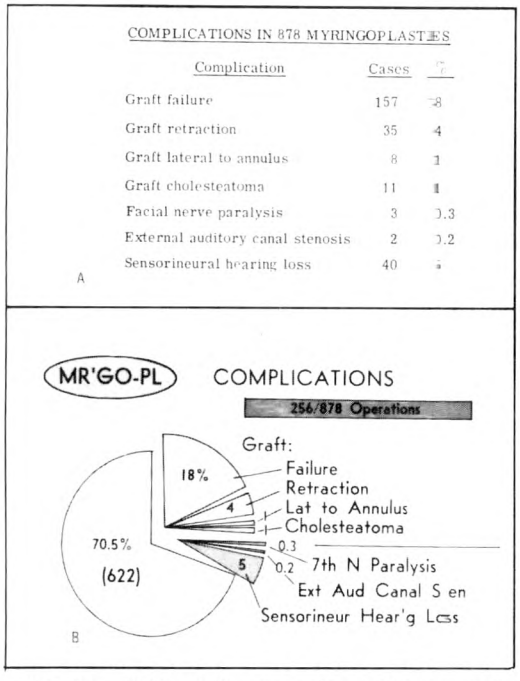


MYRINGOPLASTY
Hearing Results in 340 Operations

Graft material	Oper., no.	Air conduction at or < 30 dB level, %	Air-bone gap closed to within 15 dB, %	Air-bone gap closed to within 10 dB, %
Canal skin and fascia	133	77	59	32
Single fascia	76	78	63	42
Double fascia	76	87	76	50
Canal skin	44	75	68	45
Canal skin and homograft MT	11	73	64	18
Total	340	79	65	40

B

FIG 10. Bar graph (*A*) conveying—more easily—same information as table (*B*), which is too large anyway. (Abbreviations will be explained by the speaker.)



COMPLICATIONS IN 878 MYRINGOPLASTIES

Complication	Cases	%
Graft failure	157	18
Graft retraction	35	4
Graft lateral to annulus	8	1
Graft cholesteatoma	11	1
Facial nerve paralysis	3	0.3
External auditory canal stenosis	2	0.2
Sensorineural hearing loss	40	5

A

FIG 11. Table (*A*) expressing relations more readily grasped from pie chart (*B*).

the original copy on high-contrast black-and-white 35-mm film and, after processing for proper density, printing on diazo sheets by exposure to ultraviolet or high-intensity lights. Exposure destroys the dye potential in the diazo sheet where light passes through the negative (the text portions); and as the background receives no exposure, it takes on color from "fuming" (exposure to ammonia vapor). Although diazo sheets are available in a variety of colors, blue has been most widely accepted.

For those who wish to carry through the entire process from original to slide, an easily managed, photographic device the Visualmaker,[5] is available. An Eastman Kodak Company product, it provides for slide making by use of color film for both black-and-white and color originals. There are two standard formats: a 75-mm (3-inch) square and a 200-mm (8-inch) square. Excellent

FIG 12. (Courtesy of John W. Desley, Medical Graphics, Mayo Clinic and Mayo Foundation.)

suggestions for the preparation of originals are provided. If these recommendations are observed, along with suggestions offered earlier, this technique yields acceptable slides.

In summary, slides intended for presentation with a paper require special consideration—a textbook-type illustration will not qualify. Give the second look of appraisal, that of the viewer at the rear of the meeting room. Rethink, reorganize, simplify, and clarify the essential data and prepare them according to accepted legibility standards. Stand tall with viewers (fig 12) for contributing to improved visual communication.

REFERENCES

1. Matthias RC: Next slide, please. SK&F Psychiatric Reporter, November-December, 1962

2. Fuller HJ: AAAS meetings and lantern slides. Science 107:140-141, 1948

3. Kern RA: How to present a scientific paper before a large audience (editorial). Ann Intern Med 37:618-624, 1952

4. Audy JR: Delivery of papers at scientific meetings. J Biocommun 1:30-33, 1974

5. Hurtgen TP: Visual aid technics. Dent Radiogr Photogr 46:40-46, 1973

Anesthesia for Transcervical Thymectomy in Myasthenia Gravis

DIGVIJAY S. GIRNAR, MD*
AVRON I. WEINREICH, MD†
New York, New York‡

This review of anesthetic experience in 100 cases of transcervical thymectomy for myasthenia gravis (MG) at The Mount Sinai Hospital (1970-1974) underlines current trends in the surgical management at Mount Sinai, where transcervical thymectomy is the procedure of choice for all patients with nonthymomatous MG and for selected patients with thymomatous MG. The transthoracic approach is now limited to malignant thymomas and tumors not accessible through the transcervical approach. Formerly, patients coming for thymectomy either already had a preexisting tracheostomy, or an elective tracheostomy was performed at the time of thymectomy. Since 1972, none of these patients has had elective tracheostomy at the time of operation, and only four were performed in the postoperative period, patients being intubated orotracheally at the time of operation. The tube is usually removed within 1 hour after completion of thymectomy. All patients are followed in the intensive care unit for 24 hours or longer, under close supervision of experienced personnel aware of the inherent problems and able to assist ventilation at any stage. This approach has greatly changed the postoperative course of this disease.

MYASTHENIA gravis (MG) is a syndrome characterized by undue muscle weakness upon exertion of the involved muscle groups and by a partial return of function either with rest or the administration of appropriate drugs. The weakness may range from diminution of action potentials on EMG of the clinically uninvolved muscles (group I-A in modification of the Osserman classification)[1] to complete motor failure of the involved muscle groups.

Evidence is accumulating that MG is an autoimmune disease[2] and that the purpose of therapy should be directed toward interrupting or ameliorating the autoimmune process. Thymectomy, previously recommended on the basis of empirical observation, now appears to be the treatment of choice for achieving this goal.[3]

The surgical management and the ultimate outcome of the disease largely depend on the care given by a specialized team, which includes internist, surgeon, anesthesiologist, and experienced nursing staff. The anesthesiologist may be faced with unexpected and complex problems, both during the operation and in the postoperative period.

The transcervical approach for thymectomy has replaced the transthoracic in our hospital since 1967 (table 1). The simplicity of this approach has contributed to a dramatic overall reduction in morbidity and mortality in this group of patients,[4] allowing an earlier return to spontaneous respiration, permitting earlier extubation, and avoiding the necessity for tracheostomy. Surgical operation was previously recommended in

*Resident in Anesthesiology.

†Associate Clinical Professor.

‡Department of Anesthesiology, Mount Sinai School of Medicine of the City University of New York and the Mount Sinai Hospital, New York, New York 10029.

Paper received: 11/21/74
Accepted for publication: 6/18/75

TABLE 1

1958-1967	Thymectomy by transthoracic approach: All patients had elective tracheostomies at the time of thymectomy.	251 cases
1967-1971	Transcervical thymectomy: All patients had elective tracheostomy at the time of thymectomy. Transthoracic thymectomy was performed in cases of: (a) Thymoma (b) Preexisting low-lying tracheostomy	200 cases
1972-1974	Transcervical thymectomy: No elective tracheostomy.	151 cases

those patients with severe symptoms who had become refractory to anticholinesterase drugs. As a result of reduced operative mortality and morbidity with the transcervical approach, the indications for thymectomy have been expanded to include the milder cases and those with a shorter history of the disease.[3,4]

Clinical Experience. — At The Mount Sinai Hospital between January 1970 and March 1974, 151 patients underwent thymectomies. One hundred of these, ranging in age from 6 to 70 years and including 36 males and 64 females, for whom records were complete, have been classified[5] according to their myasthenic severity:

Pediatric group:

a. Neonatal—occurs only in infants born of myasthenic mothers and is self-limiting.

b. Juvenile—may develop at any time from birth to puberty.

Adult group:

1. (a) Ocular myasthenia. This localized form of the disease may be limited to one eye and is characterized by ptosis and diplopia.

2. (a) Mild generalized MG. This group is characterized by slow onset, frequently ocular.

   (b) Moderate generalized MG. Onset is gradual, with ocular presentation progressing to a severe generalized involvement of bulbar and skeletal musculature and with involvement of respiratory muscles.

3. Acute fulminating MG. Rapid onset of severe bulbar and skeletal muscle weakness with involvement of respiratory musculature.

4. Late severe MG. Severe myasthenia develops at least 2 years after the onset of group 1 or 2 symptoms. Progression of the disease may be sudden or gradual.

ANESTHETIC MANAGEMENT

Preoperative Visit.—This is mandatory for the attending anesthesiologist, since these patients as a group tend to be anxious and aware of their condition, and require assurance and full explanation of the procedure. The need for possible postoperative ventilatory support is explained carefully, and whenever possible the patient is introduced to the members of the intensive care unit who will be caring for him. Sedation is prescribed as necessary, the results of the routine investigations are checked, and any deviations from normal in any of the parameters are corrected prior to operation. A respiratory system review should observe the absence of chest infection and include an estimate of exercise tolerance. Emergency drugs and equipment for intubation are kept within reach.

Premedication.—Half of the morning dose of pyridostigmine is given in mild cases (classes 1 and 2) while in more severe cases, the regular morning dose is prescribed IM. Atropine (0.4 to 0.6 mg IM) is given 1 hour before operation. Various combinations of narcotics, barbiturates, or tranquillizers are used.

Induction.—On arrival in the operating room an IV infusion is started; temperature, ECG, and blood pressure are recorded. A sleep dose of sodium thiopental is given, and halothane or enflurane and N_2O-O_2 are given by mask. Once the patient is well anesthetized and the masseters are relaxed, an attempt is made to visualize the vocal cords,

which are then sprayed with 4 percent lidocaine, and the patient is subsequently intubated with a nonkinkable anode tube.

Should there be any difficulty with intubation, anesthesia is deepened and a further attempt at intubation is made. After auscultation has determined that both sides of the chest are being aerated, the tube is secured and the patient is mechanically ventilated. The eyes are taped and the head is fully extended with sheets under the shoulders. The patient is positioned and draped as for a standard head and neck procedure. The surgeon stands behind the patient's head.

The incision is made across the suprasternal notch, and a fiberoptic light is used to aid in visualization of structures deep to the sternum. Once the bilobed thymus has been removed entirely and hemostasis achieved, the wound is closed in layers and drained with a Hemovac.®[4] At the end of the procedure, an attempt is made to reestablish spontaneous ventilation and the patient is taken to the intensive care unit, breathing 100 percent O_2 spontaneously via the endotracheal tube or is assisted with an Ambu® bag.

Postoperative Procedure.—On admission to the intensive care unit (ICU), respiratory data are collected on all patients. Routinely, a Wright respirometer is used and tidal volume, minute volume, vital capacity, and respiratory rate are recorded. Blood is drawn from the radial artery for Pao_2, $Paco_2$, pH, base excess, and hematocrit, to establish baseline data. Chest x-rays are routinely taken on ICU admission and thereafter as indicated by the patient's condition. If secretions are copious and troublesome due to the bronchorrhea produced by the anticholinesterase therapy, combined suctioning and chest physiotherapy is employed and atropine administered IV, as needed.[6]

Depending upon the severity of the disease, those who were breathing spontaneously preoperatively are usually extubated once they are fully awake and exchanging adequately, usually within the 1st hour after operation. A resuscitation tray is kept at the head of the patient's bed and a ventilator is kept beside it, in case the patient's condition should deteriorate.

Some patients have had to be weaned off the ventilator gradually, depending on their clinical response. The psychologic aspects cannot be stressed too strongly, as these patients as a group are very dependent on the medical and nursing staff and require constant reassurance and encouragement.

Where secretions remain troublesome, and particularly where respiratory infection supervenes, a tracheostomy may be indicated after 48 hours. Since 1972, 4 of our patients have required postoperative tracheostomy. In the postoperative period, once the patients are fully awake, the preoperative anticholinesterase regime is continued IM. Once they are able to swallow, oral therapy is reinstituted as indicated.

Of the 100 patients studied, all but one received thiopental for induction and the majority were intubated with halothane. Seven patients were given enflurane, introduced late in the series. Positive-pressure ventilation was maintained routinely during operation. Ninety patients of this group were able to breathe spontaneously at the end of the surgical procedure, and 92 were extubated within 2 hours after operation. The average duration of surgery was 2 hours.

DISCUSSION

The value of thymectomy in the treatment of MG is well established, and remissions are generally permanent, the percentage of patients in remission increasing yearly. Of 111 nonthymomatous myasthenic patients followed for 7 years, 90 percent were in remission or showed marked improvement.[2]

It is generally accepted that the thymus is responsible for the formation of antibodies. The thymic hyperplasia with germinal center formation and/or spindle-cell thymomas is a consequence of this increased thymic activity.[2] The theory to which we currently subscribe is that the stable remission produced by thymectomy is presumably the result of eliminating the germinal centers responsible for the formation of these antibodies.[2] The nature of the autoimmune response at the myoneural junction is still not clear. Though spontaneous remissions do occur in myasthenics on medical treatment, they are generally followed by relapses.

In this institution from 1958 onward, all patients admitted for transthoracic thymectomy either had had a preoperative tracheostomy or underwent routine tracheostomy at the time of thymectomy, to cope with secretions and offer a route for ventilatory

assistance. In 1967, the transcervical approach was introduced, and the routine performance of elective tracheostomy was continued until 1971. Since 1972, no elective tracheostomy has been performed. Experience in recent years, with prolonged oral and nasotracheal intubation, using nonreactive materials and low-pressure cuffs, has markedly reduced the incidence of tracheal erosion and has influenced us to adopt this method. This development went hand in hand with the establishment of an ICU, where a team skilled in the care of such patients provides the single most important factor in determining a successful postoperative outcome.

Though complications of transcervical thymectomy are rare, they need to be mentioned:

1. Hemorrhage involving the great vessels of the mediastinum at the time of operation.

2. Pneumothorax: A small pneumothorax is not uncommon; an immediate postoperative chest x-ray will reveal its extent and indicate the need for aspiration.

3. Air embolism is a remote possibility, but none occurred in this series and none has been reported.

Narcotics, sedatives, or tranquilizers as premedication should be used with circumspection, to avoid respiratory depression or the ability to cope with secretions.

The use of pyridostigmine preoperatively to avoid a respiratory crisis from developing at this time may lead to difficulty in intubation without relaxants in a patient who manifests no weakness. The excessively deep levels of halothane required for intubation frequently produces an undesirable fall in blood pressure. In the 7 cases for which we employed enflurane, we have the impression that earlier and better relaxation of the masseters was achieved, though the laryngeal reflex is not as well obtunded as with halothane. The use of topical 4 percent lidocaine will, however, permit early intubation in these cases. Should the need arise for further relaxation, a small amount of d-tubocurarine (0.5 to 1 mg at a time) may be given until the desired degree of relaxation is achieved.

No attempt is made to reverse the neuromuscular block at the end of the operation, and the patient remains intubated to the intensive care unit. To facilitate intubation, we propose to eliminate the morning dose of pyridostigmine in those patients with mild generalized MG, though many myasthenics are so psychologically dependent that they may still require a placebo.

The myasthenic condition may be worsened by a large variety of drugs having a synergistic effect with the defect in neuromuscular transmission or aggravating the muscarinic effects of anticholinesterase therapy. Some of the more frequently encountered drugs are reviewed in table 2, together with the possible mode of action in this as yet not very well elucidated field.

CONCLUSIONS

Transcervical thymectomy for MG and the routine use of endotracheal intubation with postoperative care in an intensive care unit represents a significant advance. These have all but eliminated the need for tracheostomy and have further decreased the morbidity and mortality in this condition when surgical operation is undertaken in the earliest stages of the disease.

REFERENCES

1. Osserman KE, Genkins G: Critical reappraisals of the use of edrophonium test in myasthenia gravis and significance of clinical classification. Ann NY Acad Sci 135:312-316, 1966

2. Papatestas AE: Studies in myasthenia gravis: effects of thymectomy. Amer J Med 50:465-474, 1971

3. Papatestas AE: The effect of thymectomy on the prognosis in myasthenia gravis. Mount Sinai J Med 6:586-593, 1971

4. Kark AE: Total thymectomy by transcervical approach. Sur Br J Sur 58:321-326, 1971

5. Osserman KE: Studies in myasthenia gravis—review of a twenty year experience in over 1,200 patients. Mount Sinai J Med 38:538-572, 1971

6. Bryan-Brown C: Contributions of the intensive care unit in the care of the myasthenia gravis patients. Mount Sinai J Med 6:573-579, 1971

7. Goodman L, Gilman A: The Pharmacological Basis of Therapeutics. Fourth edition McMillan Publishing Company, New York 1970, pp 1118-1119

8. Schmidt JL, Vick NA: The effect of quinidine on the action of muscle relaxants. JAMA 183: 669-671, 1963

9. Drachman DA, Skom JH: Procainamide a hazard in myasthenia gravis. Arch Neurol 13:316-320, 1965

10. Foldes FF, McNall PG: Myasthenia gravis: a guide for anesthesiologists. Anesthesiology 23:837-869, 1962

TABLE 2

Drugs to Avoid or Use with Caution in Myasthenia Gravis

1. *Muscle relaxants:* The site of action and the effects of the depolarizing and nondepolarizing agents are well elucidated and should be used cautiously. Synergism occurs with the nondepolarizers and while initial antagonism to the depolarizers occurs, it may be followed by a prolonged apnea in the patients treated with anticholinesterases.

2. *Antiarrhythmic agents:* May produce a profound deterioration in the myasthenic state, quinine[7] and quinidine[8] by decreasing the spread of excitation along the muscle fiber; procainamide[9] by decreasing the amount of acetylcholine liberated at postganglionic endings.

The myocardium may be involved in the disease process, and arrhythmias are not uncommon. In addition, irregularities may occur with the use of halogenated inhalation agents in the presence of large doses of anticholinesterase drugs. Digitalis, diphenylhydantoin, or lidocaine may be safely employed.

3. *General anesthetics:* Have both central and peripheral actions. Ether, enflurane, methoxyflurane have all been used. Ether has a curarelike effect at the myoneural junction; owing to its irritant effect on the tracheobronchial tree, it is generally not recommended, although Foldes[10] has suggested its use in low analgesic concentrations with N_2O-O_2, as its myoneural effects are more transient than those of the nondepolarizing relaxants. Cyclopropane is strongly vagotonic, and together with anticholinesterases may increase the incidence of arrhythmias. No flammables can be used in the presence of diathermy, which is now universally employed.

4. *Local anesthetic agents:* One should avoid high concentrations of ester-linked local anesthetics hydrolyzed by nonspecific cholinesterases of plasma and liver. This enzyme is inhibited by anticholinesterases, and the toxicity of these agents may be significantly increased in myasthenic patients on pyridostigmine bromide, a long-acting anticholinesterase.[10]

5. *Narcotics:* The depressant effects of morphine[11] sulfate are enhanced by anticholinesterase therapy. Judicious use is recommended, especially in the postoperative period, and while there is usually no need for narcotics in premedication, about 15 percent of MG patients have marked painful sensory involvement.

6. *Barbiturates:* Pentobarbital sodium, secobarbital sodium, and phenobarbital sodium have both central and peripheral effects. While they are used both as premedication and for induction, large doses may have an adverse effect on neuromuscular conduction in MG patients by rendering the postsynaptic membrane insensitive to acetylcholine.[12]

7. *Tranquillizers:* Myasthenics are emotionally labile as a group and often need tranquillizers. Chlorpromazine intensifies the effects of d-tubocurarine and gallamine.[13] Meprobamate and diazepam probably depress transmission of nerve impulse in the cord.[14]

8. *Antibiotics:* Streptomycin, neomycin, kanamycin, gentamycin, sulfonamide, and colistin derivatives (Coly-Mycin,® Cleocin®) all reduce the total amount of acetylcholine released. Part of the mechanism lies in their depletive action on calcium, which plays a role in the release of the acetylcholine quanta.[15,16]

9. *Antihypertensives:* Guanethidine, hexamethonium, and trophenium all potentiate the effects of depolarizing muscle relaxants. MAO inhibitors have a similar effect.[17]

10. *Diuretics:* Such agents as thiazides and furosemide have a potassium-depleting effect, thereby enhancing muscle weakness.

11. *Electrolytes:* Low sodium,[18] low calcium, and high magnesium[19] interfere with release of acetylcholine.

11. Bergh NP: Reactions of patients with myasthenia gravis to different agents causing a neuromuscular block. Scand J Clin Lab Invest 5:1-47, 1953

12. Thesleff S: The effects of anaesthetic agents on skeletal muscle membrane. Acta Physicl Scand 37:335-349, 1956

13. Dyberg V, Hongs W: Investigations into combined effects of chlorpromazine and neuromuscular blocking agents cn red and white muscles. Acta Pharmacol 14:130-137, 1958

14. Wilson VJ, Talbot WH: Recurrent condition in the cat spinal cord—differential effect of meprobamate on recurrent facilitation and inhibition. J Gen Physiol 43:495-502, 1960

15. Hokken E: The aggravating effect of some antibiotics on the neuromuscular blockade in myasthenia gravis. Acta Neurol Scand 40:346-352, 1964

16. Sabawala PB, Dillcn JB: The action of some antibiotics on the human intercostal nerve muscle complex. Anesthesiology 20:659-668, 1959

17. Bodley PO, Holwax K, Potts L: Low pseudocholinesterase levels complicating treatment with phenelazine. Brit Med J 3:510-512, 1969

18. Nastuk WL: Relationship between extracellular Na and depolarizing action of acetylcholine cn end-plate membrane. Fed Proc 13:104, 1954

19. Del Costilo J: The nature of the neuromuscular block produced by magnesium. J Physiol 124:370-384, 1954

Changes in Airway Resistance Following Droperidol, Hydroxyzine, and Diazepam in Normal Volunteers

JAMES E. COTTRELL, MD*
BERNARD WOLFSON, MB, FFARCS†
E. S. SIKER, MD‡

The effects of droperidol, hydroxyzine, and diazepam on airway resistance (AR), functional residual capacity (FRC), and thoracic gas volume (TGV) were compared, using a CPI model-2000 body plethysmograph.

Significant decreases in AR were seen following droperidol and hydroxyzine at all time intervals. A significant increase in AR also was noted 90 minutes after diazepam injection. FRC significantly decreased at 60, 90, 120, and 150 minutes following droperidol, and at 90 minutes following hydroxyzine, while no change was seen following diazepam.

No significant changes in TGV were seen following administration of any of the drugs.

THE armamentarium of the anesthesiologist now includes a large number of psychotropic drugs. Although they are used primarily for their central nervous system effects, the possibility of useful or deleterious effects on other systems must be considered.

Recently, Steen and associates[1] compared the effects of diazepam and hydroxyzine on airway resistance (AR) and thoracic gas volume (TGV) in patients with bronchospastic disease. They found that hydroxyzine significantly reduced both AR and TGV, while diazepam had no significant effect on either parameter.

The present study was undertaken to compare the effects of hydroxyzine, diazepam, and droperidol on AR in volunteers with normal respiratory systems.

METHOD

Eight volunteers, 2 women and 6 men, with normal pulmonary function (FEV_1 greater than 70%, FEV_3 greater than 95%, vital capacity greater than 80% of the predicted), measured with a National Cylinder Gas Pulmonary Function Indicator, took part in the study. Ages ranged from 24 to 29 years and weights from 45 to 80 kg. None of the volunteers had a prior history of bronchospastic disease.

Using a Cardio-Pulmonary Instruments Corporation model-2000 body plethysmograph, AR, simultaneous TGV, and FRC were measured before intramuscular injection of either hydroxyzine (1 mg/kg), diazepam (0.1 mg/kg), or droperidol (0.07 mg/kg). Measurements were repeated at 30, 60, 90, 120, 150, and 180 minutes after drug injection. Each subject was given three injections, one of each drug, with 7 or more days between injections. In addition, one subject received an additional dose of hydroxyzine following the three injections. Neither the subjects nor the investigator knew which drug had been administered.

The plethysmograph consists, in essence, of a sealed box, within which pressure

*Assistant Professor of Anesthesiology, Department of Anesthesiology, New York University Medical Center, New York, New York 10016.

†Director of Anesthesia Research, Mercy Hospital, Pittsburgh, Pennsylvania.

‡Chairman, Department of Anesthesiology, Mercy Hospital, Pittsburgh, Pennsylvania.

Paper received: 4/30/75
Accepted for publication 6/17/75

TABLE 1

Changes in Airway Resistance (cm H_2O/L/sec) Following IM Injection of Hydroxyzine, Diazepam, and Droperidol

Time (minutes after injection)	Hydroxyzine (8 subjects)		Diazepam (8 subjects)		Droperidol (4 subjects)	
	Mean ± SD	$p =<$	Mean ± SD	$p =<$	Mean ± SD	$p =<$
Control	1.88 ± 0.11		1.86 ± 0.10		1.80 ± 0.15	
30	1.40 ± 0.15	0.0125	1.94 ± 0.11	0.3	1.19 ± 0.10	0.01
60	1.05 ± 0.16	0.0005	2.02 ± 0.10	0.15	0.96 ± 0.08	0.0025
90	0.071 ± 0.15	0.0005	2.15 ± 0.12	0.05	0.86 ± 0.07	0.0025
120	0.88 ± 0.12	0.0005	2.06 ± 0.12	0.15	0.81 ± 0.11	0.0025
150	1.29 ± 0.14	0.0025	1.98 ± 0.12	0.25	0.98 ± 0.09	0.0025
180	1.57 ± 0.12	0.05	1.92 ± 0.11	0.35	1.04 ± 0.12	0.005

changes are measured, and a pneumotachygraph, through which the seated subject breathes and from which flow measurements are derived. In addition to box pressure, pressure may be measured at the subject's mouth. Using Boyle's Law, it is possible to calculate lung volumes via the pressure recorded. When flow rates are known, AR may be calculated. Lung volumes measured by this technic include all gas within the chest, including trapped gas, in contradistinction to the more usual closed-circuit helium technic,[2] which measures only gas in full communication with patent airways.

RESULTS

The following results apply to 8 subjects in the hydroxyzine and diazepam group but to only 4 subjects in the droperidol group, because of unpleasant side effects including restlessness, irritability, and insomnia, as previously reported.[3]

1. Airway Resistance.—Hydroxyzine significantly reduced AR at each time interval throughout the study period, the greatest reduction being seen 90 minutes after injection of the agent (table 1). Diazepam caused a significant rise at 90 minutes and droperidol was followed by a significant reduction at each time interval, the greatest effect being seen at 90 and 120 minutes.

2. Functional Residual Capacity.—A reduction in FRC followed both hydroxyzine and droperidol, statistically significant at 90 minutes following hydroxyzine and at 60, 90, 120, and 150 minutes following droperidol. Diazepam caused no significant change in FRC (table 2).

3. Thoracic Gas Volume.—Insignificant changes followed administration of hydroxyzine, droperidol, and diazepam (table 3).

DISCUSSION

The reciprocal of resistance is conductance. It follows that conductance increases as lung volume increases. If conductance is divided by lung volume, conductance/liter

TABLE 2

Changes in Functional Residual Capacity (ml) Following IM Injection of Hydroxyzine, Diazepam, and Droperidol

Time (minutes after injection)	Hydroxyzine (8 subjects)		Diazepam (8 subjects)		Droperidol (4 subjects)	
	Mean ± SD	$p =<$	Mean ± SD	$p =<$	Mean ± SD	$p =<$
Control	2175 ± 117		2167 ± 115		2224 ± 186	
30	2093 ± 122	0.35	2186 ± 116	0.45	2025 ± 184	0.25
60	1945 ± 113	0.10	2164 ± 119	0.49	1718 ± 141	0.05
90	1792 ± 110	0.025	2176 ± 120	0.48	1722 ± 145	0.05
120	2006 ± 120	0.20	2167 ± 118	0.5	1754 ± 159	0.05
150	2070 ± 124	0.30	2163 ± 120	0.45	1785 ± 130	0.05
180	2127 ± 121	0.40	2153 ± 119	0.48	1817 ± 144	0.10

TABLE 3
Changes in Thoracic Gas Volume (ml) Following IM Injection of Hydroxyzine, Diazepam, and Droperidol

Time (minutes after injection)	Hydroxyzine (8 subjects) Mean ± SD	$p =<$	Diazepam (8 subjects) Mean ± SD	$p =<$	Droperidol (4 subjects) Mean ± SD	$p =<$
Control	5280 ± 312		5278 ± 311		5360 ± 512	
30	5208 ± 315	0.45	5287 ± 314	0.45	5167 ± 441	0.40
60	4820 ± 326	0.20	5290 ± 314	0.045	4610 ± 437	0.15
90	4665 ± 338	0.10	5295 ± 314	0.49	4473 ± 422	0.15
120	5128 ± 315	0.40	5292 ± 312	0.49	4900 ± 431	0.30
150	5186 ± 321	0.45	5292 ± 5281	0.49	5915 ± 406	0.25
180	5215 ± 310	0.35	5281 ± 313	0.49	4840 ± 401	0.25

is obtained, and this is perhaps the most valid measurement to use when assessing effects on AR, as changes due to lung volume are eliminated. Because lung volume and resistance were decreasing at the same time in this study following hydroxyzine and droperidol, changes in conductance/liter were very marked, as seen in the figure.

There has been much discussion in the literature about the respiratory effects of these drugs, especially alterations in the CO_2 response curve; however, little information is available regarding their effect on bronchiolar smooth muscle tone. Steen found negligible the effect of diazepam on AR in asthmatics, while Heionen and Muittari[4] reported subjective improvement in asthmatics but no change in AR.

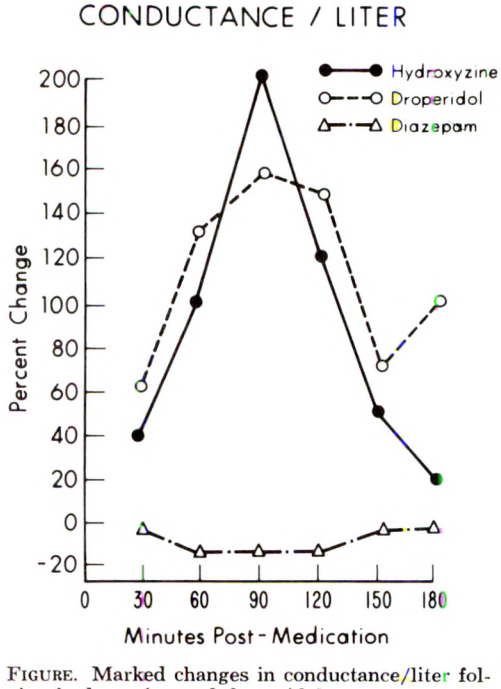


FIGURE. Marked changes in conductance/liter following hydroxyzine and droperidol.

When used alone, droperidol has been shown by MacDonald and coworkers[5] to be devoid of significant respiratory effects, Stocker[6] reported that droperidol had no appreciable effects on bronchial size, and several studies[7-9] have suggested that droperidol may have alpha-adrenergic-blocking properties. Both beta- and alpha-adrenergic receptors are thought to be present in bronchial smooth muscle. Stimulation of beta receptors and treatment with alpha-blocking agents cause bronchodilation.[10] These responses might explain the marked increases we found in conductance following droperidol administration.

The most outstanding effect of hydroxyzine on respiratory parameters is that already referred to by Steen's group. It is of some interest that the maximum effect on conductance/liter reported by Steen was an increase of 60%. This must be compared with the present results, where the peak increase was 200%, suggesting that hydroxyzine may be even more effective in dilating normal air channels than spastic ones. No correlation between hydroxyzine and adrenergic effects has been demonstrated.[11]

Steen's study appears to indicate that hydroxyzine is valuable in the asthmatic patient. However, its value in the normal patient depends on the alterations produced in the closing volume (CV)/FRC ratio. Much attention has been paid recently to the concept of CV and its relationship to FRC as a cause of intraoperative and postoperative hypoxemia.

Don and colleagues[12] showed that both the supine position and the induction of anesthesia cause a fall in FRC. Recently they provided evidence to suggest that this alteration in FRC may lead to a reversal of the normal CV/FRC relationship (CV less than FRC) and may thus lead to air trapping, the functional effect of which is impairment of gas exchange.

It has also been shown recently by Craig and McCarthy[13] that positive-pressure breathing increases both CV and FRC but that FRC is increased more than CV. Both components of FRC—expiratory reserve volume (ERV) and residual volume (RV)—were increased, but the increase in CV was said to be a result of the increase in RV. At the completion of the study, the injection of hydroxyzine was repeated in one subject and spirometric readings were made in addition to the plethysmographic, in an effort to investigate further the fall in FRC, which was found due to a reduction in the RV component.

REFERENCES

1. Steen SN, Crane R, Thomas JS: Effects of Intramuscular Hydroxyzine on Specific Airway Conductance of Patients with Chronic Bronchospastic Disease (Asthma). Scientific Abstracts, American Society of Anesthesiologists Annual Meeting, Atlanta, 1971, pp 85-86

2. Comroe JH, Forster RE, DuBois AB, et al: The Lung. Second edition. Chicago, Year Book Medical Publishers, Inc, 1971, pp 16-17

3. Clark MM: Droperidol in pre-operative anxiety. Anaesthesia 24:36-37, 1969

4. Heinonen J, Muittari A: The effect of diazepam on airway resistance in asthmatics. Anaesthesia 27:37-40, 1972

5. MacDonald HR, Braid DP, Stead BR, et al: Clinical and circulatory effects of neurolept analgesia with dehydrobenzperidol and phenoperidine. Br Heart J 28:654-662, 1966

6. Stocker L: The effect of anesthesiologic premedication. Effects of conventional premedicating agents (pithidine, promethazine, diazepam, dehydrobenzperidol, fentanyl, thalamonal) on bronchial resistance and respiration in the human. Anesth Abstract, Chir Klin, Essen, Ruhr Univ, Bochum-Fortschr Med 88:1121-1122, 1970

7. Yelnosky J, Katz R, Dietrich E: A study of some of the pharmacologic action of droperidol. Toxicol Appl Pharmacol 6:37-47, 1964

8. Prys-Roberts C, Kelman GR: The influence of drugs used in neuroleptanalgesia on cardiovascular and ventilatory function. Br J Anaesth 39:134-145, 1967

9. Whitnam JG, Russell WJ: The acute cardiovascular changes and adrenergic blockade by droperidol in man. Br J Anaesth 43:581-591, 1971

10. Aviado DM: Regulation of bronchomotor tone during anesthesia. Anesthesiology 42:68-80, 1975

11. Goldberg SJ, Linde LM, Gall PG, et al: The pulmonary and systemic hemodynamic effects produced by meperidine and hydroxyzine. J Pharmacol Exp Ther 159:306-313, 1968

12. Don HF, Craig DB, Wahba WM, et al: The measurement of gas trapped in the lungs at functional residual capacity and the effect on posture. Anesthesiology 35:582-590, 1971

13. Craig DB, McCarthy DS: Airway closure and lung volume during breathing with maintained airway positive pressures. Anesthesiology 36:540-543, 1972

PLASMA DIAZEPAM LEVELS AFTER SINGLE-DOSE ORAL AND IM ADMINISTRATION. Plasma diazepam levels were estimated by gas-liquid chromatography following a single 10-mg dose given orally (n = 40) or IM (buttocks, 41; thigh, 33) to fit young (mean 32 years) patients for minor gynecologic operations. The highest levels followed oral administration, reaching a peak at 60 minutes. Injection into the thigh resulted in a more rapid initial rise than oral or buttock. The study reinforces an earlier conclusion that, because of unacceptable pain from IM injection, diazepam should be given orally when possible. If IM must be used, deep gluteal is preferable to fascia lattal. *(Gamble, Dundee, Assaf. Anaesthesia 30:164-169, 1975.)*

In each issue of the Journal an article of particular interest and value to anesthesiologists, which has been published elsewhere, will be presented. Primarily the material will contain fundamental basic information which has been presented by anesthesiologists, physiologists, pharmacologists, and others and, on occasion, by commercial firms. In the last instance, these reprintings are not to be construed as an endorsement of the particular commercial firm or its product by Anesthesia and Analgesia—Current Researches.

The Author's Editor

BARBARA G. COX
Consultant, Section of Publications

When a physician or scientist and his editor work together on a personal basis, a creative interaction takes place. The talents of both merge to generate a superior product. And the effectiveness of this symbiotic relationship is enhanced over time. That is, as the author and editor collaborate on more projects, both the quality of the manuscripts and the efficiency of the writing process improve. Ultimately, this means that many hours of the author's time are freed for his scientific endeavors, the institution saves money, and the published material is superior.

FOR the physician or scientist who writes, the editor may be a shadowy being—a faceless entity whose cryptic notes deface the once-tidy pages of a manuscript. Or the editor may be the jealous guardian of a journal, insensitive to the pearls of wisdom an author places before him. Or he may be a disembodied copy editor, capriciously altering words and phrases with no regard for the author's painstakingly conceived prose.

Few authors see editors as editors see themselves—as servants to scientists, to readers, and to the language. Moreover, I suspect that long-buried memories of high school "English composition," with the teacher's impatient criticisms pencilled in the margins, evoke unconscious images in many authors' minds—images of the humorless scholar, more anxious to find fault than to help.

EDITORS: THE GENUS AND THE SPECIES

Editors, like authors, cannot be neatly pigeonholed. They come in different shapes, sizes and temperaments. Indeed, there are two main species of scientific editors, not to be confused with each other. One is the journal or book editor—usually first a scientist and second an editor. This kind of editor rarely revises and polishes a manuscript for publication. Generally, he has been raised to his editorial post on the basis of his scientific eminence and not because he is a student of the language.

On the other hand, the men and women to whom I refer as "authors' editors" or "professional editors" are specialists in biomedical communications. They should be professional helpmates to scientists, that is, partners in communication. These editors work to lighten the load of the scientist who

Reprinted with permission from *Mayo Clinic Proceedings* and the author.

often labors long hours into the night on a manuscript—because he cannot find 15 consecutive minutes to work on it during the day. They realize how difficult it can be for a scientist to disengage himself from the masses of data with which he is intimately familiar and to stand back to view his magnum opus from a reader's perspective. Quite apart from their ability to render an author's prose grammatically correct, skilled editors appreciate the necessity to help an author guide his readers confidently, logically, and persuasively from the beginning of his story to the end.

AUTHOR-EDITOR RAPPORT

Obviously, editorial assistance of this magnitude is not easily given without some interpersonal transactions. For most authors and editors to work effectively as a team, they must know each other. Many institutions provide their scientists with author's editors. But even then, a surprising number of authors fail to make optimum use of this resource, out of apparent ignorance of what a professional editor can do to enhance the quality of their manuscripts and an unawareness of the importance of author-editor rapport to this process. Such authors send their papers through the interoffice mail to the editorial department solely for grammatical and syntactical review. Authors in institutions that have no editorial department are frequently surprised to learn that professional editors even exist. Increasing numbers of authors who are aware of this resource locate free-lance editors* or seek the help of consulting firms in biomedical communications (a new and flourishing business in large, metropolitan areas).

How do these professional editors view their work? Equally important, how do they regard their working relationship with authors? And finally, how can editors help scientists meet their obligation to communicate with their peers on the printed page?

THE PLIGHT OF THE SCIENTIFIC AUTHOR

In addition to their other commitments, most physicians and scientists must write. Part of their professional obligation to the scientific community (and indirectly to society as a whole) is to communicate knowledge to others and to persuade by means of the written word—whether it be in articles for publication, books, grant applications, or reports. Even the letters and memoranda that constitute part of a day's work are important and should be instruments of clear communication. Yet, for a great many scientists, organizing thoughts into a logical sequence and putting them down on paper clearly and effectively are arduous tasks. Thus, countless hours are spent organizing, reorganizing, writing, and rewriting.

Most scientists who publish in professional journals work for large institutions, especially university medical centers. The physician in a large medical center may see patients most of the time, and the basic scientist may spend the largest part of his time in the laboratory, but each must write if he is to reach out to his colleagues—both within the institution and in the scientific community as a whole. Yet, whether we like to admit it or not, the average scientist is not trained to write. Consequently, he tends to tackle the job inefficiently, laboring through draft after draft of a manuscript before he is satisfied. Even then, he may miss his mark—and find out only when a journal referee (presumably knowledgeable in the author's field) turns a manuscript down because he has failed to grasp important points. Or an author may be told that a granting agency has rejected his research proposal on the grounds of scientific inadequacy, when actually the proposal's literary deficiencies have been more at fault. The cost of these efforts to an institution can be staggering, although they are as yet unmeasured.

WRITING AS AN INTELLECTUAL PROCESS

Writing involves a linear thought process, wherein the words are placed on paper by a system of priority. Yet many scientists

*Two major sources of access to free-lance editors in medicine and the basic sciences are the American Medical Writers Association and the National Association of Science Writers.

are relatively nonverbal. That is, much of their thinking is in images, not in words. Einstein, when asked by a colleague whether his thought processes about higher mathematical concepts were carried out in word and number images or in visual images, replied that he definitely thought in visual images.

Writing a scientific report involves a sort of translation process from images to words. Moreover, the scientist must consider many aspects of his work at the same time. Thus, many thoughts and images play across his conscious mind either simultaneously or over a short space of time. He does not always sort his ideas out in linear form, the way ideas must be sorted to be presented most effectively on paper. Consequently, when he sits down at his desk, pen in hand, he may be frustrated because he must make his pen speak the language of the printed page. He finds that he cannot lift the scenes from his head and lay them on paper easily and painlessly.

THE PROFESIONAL EDITOR AS AN INSTITUTIONAL RESOURCE

Most industries, aware of the merits of specialization, hire technical editors and writers to ease the writing burden of their scientists. Industry, traditionally more conscious of where it spends its dollars than universities, pays people to do what they do best—and only that. In this respect, the scientists in an academic setting is less fortunate than his counterpart in industry. He tends to feel that he must be many things to many men: not only scientist but teacher, administrator, and writer. This charade is burdensome to the scientist and expensive for the institution.

Indeed, many medical centers have already recognized the cost-effectiveness of hiring professional scientific editors to assist their faculty. The mere availability of an editor does not guarantee his usefulness, however. A creative interaction must take place between author and editor, and this is a learned process.

THE SYMBIOSIS BETWEEN AUTHOR AND EDITOR

From my experience, the relationship between author and editor is most soundly established and functions best when the author and editor work together on a person-to-person basis. Of course, it is possible to edit an author's work without ever meeting him. Questions can simply be asked in the margins of manuscript pages or sent to the author in an accompanying memorandum. But many times this limits the editing process to superficial revisions. It deprives the editor of access to the author's personal feelings about the paper. Without personal consultation with the author, the editor may be unable to find out where the emphasis in a paper really lies or to fill in gaps that the author unwittingly leaves. Moreover, some authors react defensively to editorial criticisms pencilled on the typed page.

Several steps are involved in a productive author-editor relationship. If an author has never consulted an editor before, he may be unclear about just what an author's editor does. He may hold the common misconception that an editor "corrects the grammar, punctuation, and spelling" in the final draft of the paper. And the final draft of the paper, of course, is the product of weeks of arduous composition, revision, and polishing by the author. Yet one of the main objectives of an author's editor is to persuade the author to let go of his paper before he has invested long, needless hours in successive drafts. Provided that the thoughts are well organized, after the first draft the editor can usually revise and polish the manuscript in a fraction of the time that the author would need.

The author and editor should discuss the paper together briefly before editorial work is begun. Often, in this preliminary talk, an author will reveal major objectives of a manuscript that do not emerge clearly from the text. The author himself may have recognized weak areas in his paper and may be able to point out places where the text has bogged down. This discussion provides the editor with a better picture of the task that lies ahead.

The actual editorial process is a period of intensive analysis and revision—ranging from necessary organizational changes to simple grammatical corrections. The editor helps the author shape his paper for his intended audience, making the information flow logically and clearly. A hundred details must be attended to, as the editor strives to serve simultaneously the author, the gatekeepers of the journal or publishing house, and prospective readers.

A wise editor, as he or she works on the manuscript, remembers that authors can be

very sensitive. Many authors have become conditioned negatively by waspish queries from distant journal editors and anonymous reviewers. An author may be quick to be defensive. So a skillful editor is tactful and constructive in making criticisms. The editor and the author must be on the same team.

A final and, I believe, necessary step in the editor-author interaction during the preparation of a manuscript is a conference when the editing process has been completed. Most scientists dislike writing. Thus, when one of their revised manuscripts is returned through the interoffice mail with an editor's questions attached, it is hardly surprising that many an author simply tucks it away in a drawer for a few weeks. But if the editor sits down with an author to confer about the work, questions can be answered and the work finished without delay.

This conference with the editor accomplishes another goal. The author finds out why the editor made his changes. At minimum, this strengthens the editor-author rapport and facilitates negotiation about final changes, so that the written product represents the synthesis of two minds—the professional scientist and the professional communicator. Ideally, it helps the author learn more about sound scientific writing. It helps him identify weaknesses in his writing style. This kind of interaction enhances the efficiency of the author-editor relationship over time because the author and editor become more familiar with each other's work styles. The groundwork is laid for future cooperation.

HEIMLICH MANEUVER Food choking, although occasionally mistaken for an acute myocardial infarction, can be easily recognized as the victim cannot speak or breathe. The author reports the effectiveness of abdominal infradiaphragmatic pressure (Heimlich maneuver) in clearing an airway obstructed with particulate matter. A quick upward thrust applied on the epigastrum consistently expelled a rubber stopper from endotracheal tubes placed in anesthetized dogs. Apparently, sudden elevation of the diaphragm resulting from abdominal pressure, compresses the lungs and increases airway pressure sufficiently to dislodge obstructing material. The maneuver may also be applied to drowning victims to facilitate expelling aspirated water. Since the original description of this maneuver the author has received 162 reports of food choking or drowning victims who were "saved" by the application of infradiaphragmatic pressure. Vomiting or damage to intraabdominal organs may occur after this maneuver. *(Heimlich H: A life-saving maneuver to prevent food choking. JAMA 234:398-401, 1975)*

Some Gas Machine Hazards and Their Elimination

L. RENDELL-BAKER, MD*

Constant improvement in anesthetic gas machines has been the objective mutually of anesthesiologists, manufacturers, and engineers. Yet the literature continues to report mishaps, sometimes fatal to the patient, due to machine design or function or to "human error." The author reviews some of these hazards and describes proposals for their elimination. He points out that initiative on the part of anesthesiologists is vital in spurring needed changes by manufacturers.

Now that international agreement has been achieved by the ISO TC121† on standard 22 and 15 mm fittings for anesthesia and ventilator breathing circuits, eliminating difficulties due to multiple nonstandard fittings, the time is long overdue for action on gas machine performance and safety standards. Many papers detailing the persistent hazards and failures of our present equipment emphasize the urgency of this work now occupying anesthesiologists and engineers in the US and other countries.

As examples may be cited the recurrent problems with halothane vaporizers, starting with the 1962 report of Safar and Galla,[1] in which "the anesthetist had refilled the jar of the vaporizer inadvertently to a level 4 mm above the 'full' line" so that "the metal inflow tube extended about 1 mm beneath the fluid level causing bubbling of the N_2O-O_2 mixture through the liquid halothane." Three to four times the indicated concentration was delivered under these conditions. Prompt resuscitation saved the patient. The vaporizer was later withdrawn from sale.

This was followed in 1969 by the report of Kopriva and Lowenstein,[2] who described "a previously unreported hazard in the Verni-Trol® vaporizer." When the patient began to move during skin closure, "the halothane flowmeter valve was turned on approximately one quarter turn, but the rotameter bobbin was not seen. The flowmeter control was turned an additional quarter turn, and it was then noted that the bobbin was at the extreme top of the flowmeter. The halothane was turned off and the system flushed with O_2. At this time no pulse or heart beat was detectable." Again resuscitation was successful.

Inspection showed two of five Verni-Trol vaporizers could deliver liquid halothane when the bobbin was at the top of the flowmeter scale and the vaporizer was filled to the "maximum safe level" mark. The manufacturer provided valves to limit the pressure and flow through the vaporizer.

In 1973, Greenhow and Barth[3] reported: "While checking a . . . new Heidbrink Series DM5000 . . . machine prior to use, the O_2 flush was used to fill the circle and reservoir bag. When a breath was taken through the mask, a strong odor of halothane was noticed." With the vaporizer shunt valve open, O_2 flushing caused a rapid rise and then fall of pressure within the vaporizer, producing a surge of 2 to 3 percent halothane vapor through the delivery hose.

†International Standards Organization — Technical Committee 121, on which the USA is represented by American National Standards Institute, Committee Z79.

*Professor and Chairman, Department of Anesthesia, Mount Sinai School of Medicine, New York, New York 10029.

Paper received: 9/6/74
Accepted for publication: 6/2/75

FIG 1. Overfilling is prevented in the new Copper Kettle vaporizer (N), by placing the filler on the side of the vaporizer at the maximum safe level. The original model (O) had no mark indicating the maximum safe level, and the filler on the top did nothing to hinder gross overfilling and with it the risk that liquid agent would be delivered to the patient, with lethal effect.

The aim of the design engineer should be to eliminate as many such mechanical hazards as possible. Safety should not depend upon the user's memory and ability to carry out the correct procedure.

OTHER VAPORIZER PROBLEMS

Overfilling Hazard with Vaporizer.—The original Foregger Copper Kettle® had the filler at the top, with no indication of the maximum safe filling level. The latest model (fig 1) has the filler on the side at the maximum safe level, thus preventing overfilling. However, the Ohio Verni-Trol® still has the filler at the top, permitting overfilling; liquid agent would then be delivered to the breathing circuit with potentially lethal results.

Wrong Agent in a Kettle Vaporizer.—There is nothing to prevent an incorrect agent being added, and one is never certain what may be in a vaporizer when it has been filled by many people in a large hospital. This is a very real hazard:

"A 62-year-old white man . . . underwent an aortic-femoral bypass operation . . . with Fluothane®-N_2O-O_2 anesthesia. . . . About 6 hours after the operation, he became agitated and disoriented, with shallow respiration. Cyanosis progressed rapidly . . . the patient became comatose and died 10 hours after operation. *It was subsequently discovered that due to an error trichloroethylene, instead of Fluothane, had been placed in the Copper Kettle.* Histologic examination revealed acute necrotizing tracheobronchitis with focal intra-alveloar pulmonary hemorrhage."[4]

Safety Filling Device.—A detachable standard agent-specific filling and emptying device, like the Pin Safety System, for kettle-type vaporizers (fig 2) could solve the problem. Such a system should automatically empty the vaporizer when detached and prevent refilling until the mechanism is reattached.*

The Combined O_2 Flush-Vaporizer ON/OFF Tap used with the kettle-type vaporizer, this has resulted in accidents varying

*ANSI-Z79 proposed draft standard, Minimum Performance and Safety Requirements for Components and Systems of Continuous Flow Anesthesia Machines.

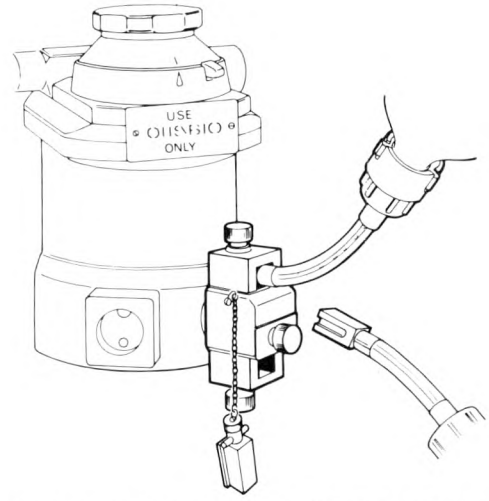


FIG 2. The Fraser Sweatman Pin Safety System. This consists of (1) a pin-indexed filling and drainage port on the vaporizer; (2) a flexible connection with a slot to match the index pin, and (3) a specific thread for the anesthetic agent container at the other end, as these containers have different diameters and threads. Overfilling is prevented also. A detachable version for kettle-type vaporizers is under study. (Fraser Sweatman, Inc illustration.)

from acute anoxia to the patient's awakening. If the vaporizer carrier gas also provides the patient's entire O_2 requirements, as may be necessary for induction with methoxyflurane, failure to turn the vaporizer on again after using the O_2 flush leads to acute anoxia, as the carrier gas is then vented to atmosphere and does not reach the patient's breathing circuit.

Unfortunately, not everyone knows this. The manufacturer became aware of this hazard, but no warning was attached to the vaporizer, and the note in the 1966 vaporizer brochure can hardly be termed explicit. According to the manufacturer's (1966) brochure, "should the anesthesiologist turn the Shunt Valve to the OFF position, he will automatically isolate the vaporizer, and the O_2 previously passing through the vaporizer *will be vented to atmosphere.* It will then be necessary to maintain a flow of metabolic O_2 from a direct O_2 flowmeter to the patient circuit. *By thus acknowledging the performance characteristics of the apparatus, the operator can fully appreciate its efficiency with complete safety.*" This final sentence must rate as a masterpiece of Orwellian "1984" logic!

Solution.—Deliver the carrier gas to the breathing circuit at all times, even though, with the tap OFF, it bypasses the vaporizer. Needless to say, the O_2 flush must always be a separate control.

Foaming of Methoxyflurane in Bubble-Through Vaporizers.—Guzman and Cascorbi[5] reported: "During induction of anesthesia, we turned on 200 ml/min of O_2, to vaporize methoxyflurane in a top-filling 400-ml Copper Kettle. This mixture was delivered to the breathing circle through a clear plastic tube which within seconds began to fill with a foamy, brownish fluid. Immediately the patient was disconnected from the machine. Since he had not inhaled any liquid, he made an uneventful recovery. The methoxyflurane had foamed in the Copper Kettle, filling the kettle and spilling foamy liquid into the delivery tube . . . a speck of sealant applied to the gasket of the lid by a professional maintenance man was responsible for turning the methoxyflurane into a foaming substance. As little as 0.004 mg of Dow-Corning #11 sealant in 100 gm methoxyflurane is enough: it will now foam when agitated. . . . We tested seven anesthetics; foam formed only with methoxyflurane, trichloroethylene, and chloroform. Methoxyflurane developed by far the most persistent foam."

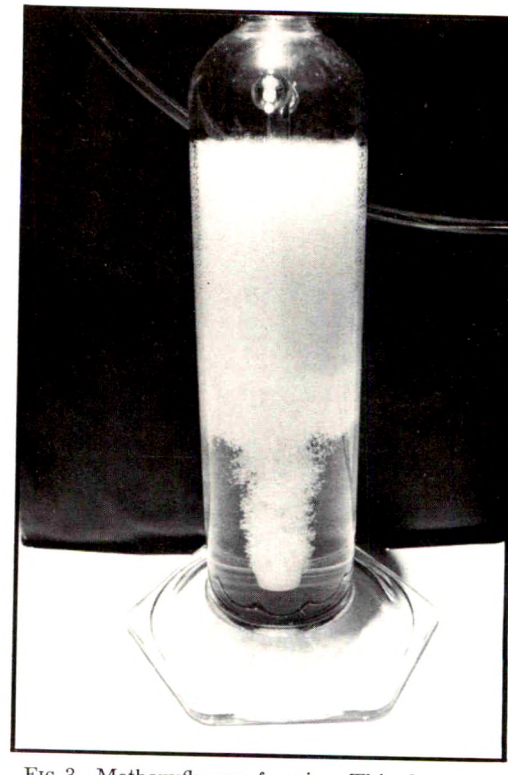


FIG 3. Methoxyflurane foaming. This demonstration by Fraser Sweatman shows the hazard if methoxyflurane in a kettle-type or bubble-through vaporizer becomes contaminated with trace quantities of a silicone compound. The foam produced readily spills over into the breathing system, as Guzman and Cascorbi reported,[5] with potentially lethal results.

Sweatman[6] subsequently reported this foam hazard was first drawn to his attention by Drs. North and Young in 1968. He later became aware that Artusio in 1959, North in 1966, Dornette in 1967, and Young in 1968 had all experienced this problem (fig 3). In 1973, Larsen[7] reviewed the problem in detail. As silicone lubricants and sealants are widely used in industry and one can never be sure they will not be used again somewhere in the assembly, can one still consider the bubble-through type vaporizer safe?

Hazard of halothane in a Pentec vaporizer. According to B. King, quoted in Fraser Sweatman, Inc, literature, halothane placed in a Pentec® methoxyflurane vaporizer in error may result in up to 30 percent halothane vapor being delivered to the breathing circuit, with potentially lethal results. The Pin Safety System filler (fig 2) would prevent this if fitted to all vaporizers, and should also prevent a vaporizer being

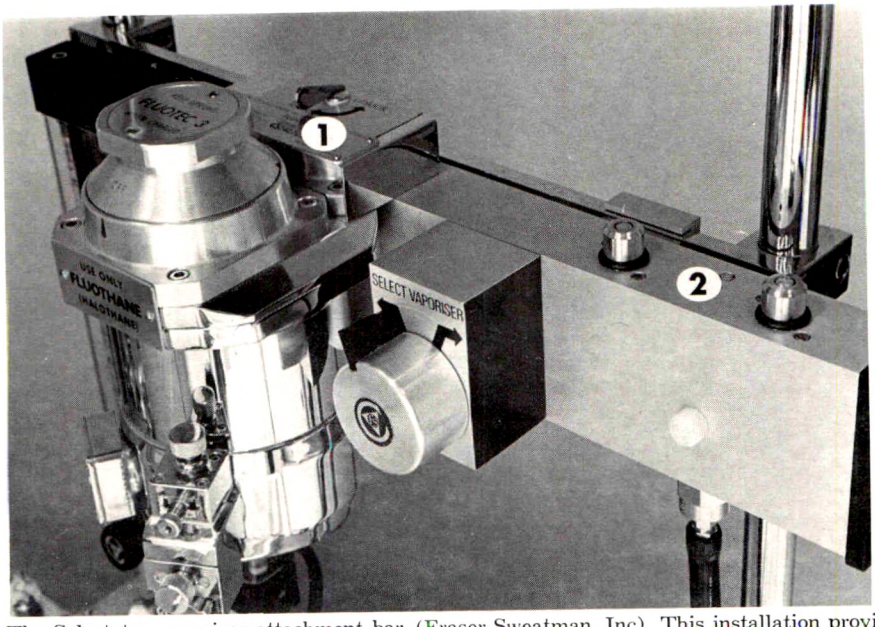


FIG 4. The Selectatec vaporizer attachment bar (Fraser Sweatman, Inc). This installation provides positions for two vaporizers at (1) and (2) but permits only one to be used at any time. Vaporizers may be readily interchanged without the use of tools.

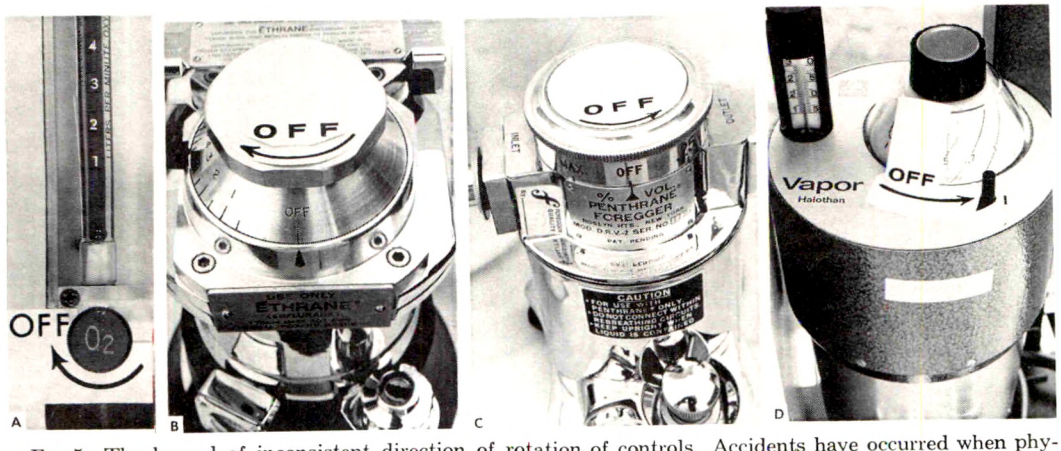


FIG 5. The hazard of inconsistent direction of rotation of controls. Accidents have occurred when physicians familiar with the counterclockwise rotation that turns off O_2 and the Fluotec vaporizer have instinctively turned the control of either a Foregger Fluomatic® or Drager Vapor vaporizer in a counterclockwise direction, under the impression that this was "OFF," when in fact this motion gave the maximum vapor concentration. It would be logical to have the direction of rotation of vaporizer controls consistent with the gas flow control valves, as there are infinitely more of the latter. (A) O_2 flow control valve; (B) Cyprane-Ethrane vaporizer; (C) Foregger Pentamatic® vaporizer; (D) Drager Vapor halothane vaporizer.

drained into a thiopental bottle, with fatal results if later given to a patient as has happened.

Vaporizers must be connected in parallel, for if two vaporizers are opened at the same time, halothane contamination of an in-series methoxyflurane vaporizer can occur.[8] In Murray's report, 7 percent halothane was found in the methoxyflurane! To prevent this, gas must NOT pass through one vaporizer after another. The Fraser Sweatman Selectatec® (fig 4) and the Drager selector systems prevent this contamination.

Should all controls rotate OFF the same way? Clockwise rotation turns OFF the O_2 and the Fluotec®, but turns ON the Foregger and Drager vaporizers—a needless accident hazard. Logically, all vaporizers must turn OFF the same way as the gas-control knobs (fig 5).

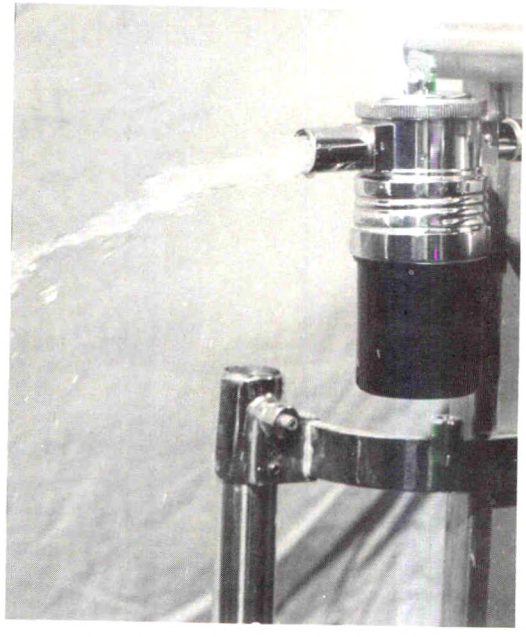


FIG 6. A "flow-critical vaporizer" can be hazardous! If this Foregger trichloroethylene vaporizer is fitted to an Ohio machine, it will empty its contents into the breathing circuit in 2 seconds, as soon as gas flows! The reason: It was designed to be attached to the *male* 15 mm common gas outlet of a Foregger machine, whereas the Ohio machine has a *female* 15 mm fitting at this location. Thus the gas flows through the vaporizer in the reverse direction to that intended by the designer.

A "Flow-Critical" Vaporizer will emit liquid agent if connected to another make of machine the wrong way (fig 6). Hopefully, no new vaporizers will be so designed. Future use of standard index-threaded fittings, permitting the component to be connected only in the correct position on the machine and the correct way, will prevent this.

FLOWMETER HAZARDS

Where's the Oxygen?—Analysis of airplane accidents shows pilot error to increase when layout of controls and instruments is inconvenient or unfamiliar.[9] Imagine the chaos if some cars had the gas pedal on the right and others had it on the left! Yet there is no standard location for the O_2 flowmeter on a machine (fig 7). The Ohio O_2 flowmeter is on the right, the Emerson-Hopkins is on the left, and the older Foregger machines have theirs somewhere in the middle! Happily, it is agreed all future US-made machines will have the O_2 on the right. But most European machines have the O_2 flowmeters on the left; and, as in Germany by law, blue is the standard color for O_2, the possibilities for confusion are legion if US and German equipment ever became intermixed.

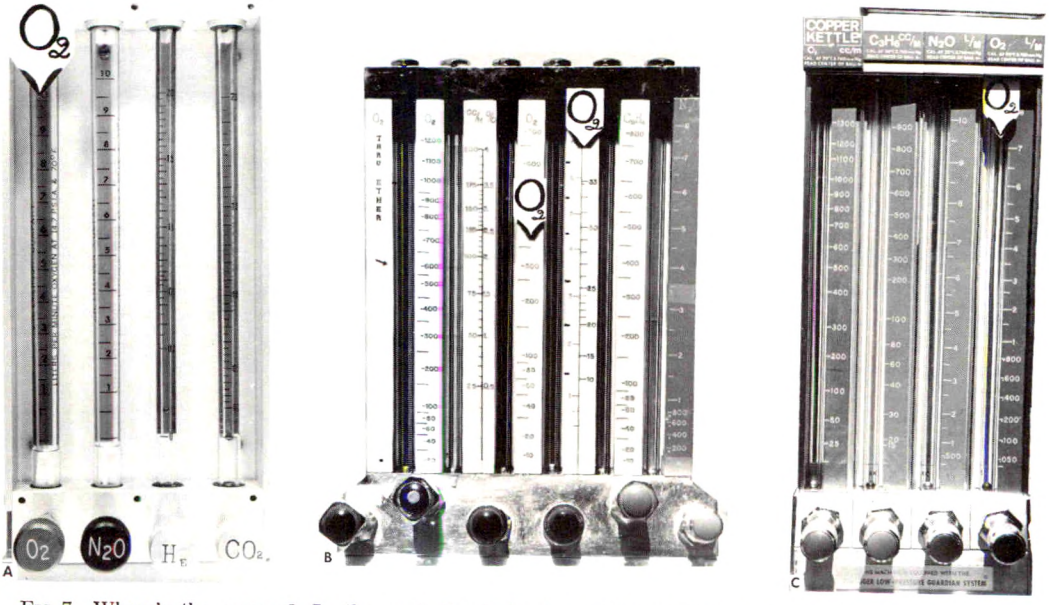


FIG 7. Where's the oxygen? In the past, the lack of a uniform location for the O_2 flowmeter has at best caused confusion and at worst injury or death of a patient. Here (A), the Hopkins-Emerson machine, has the O_2 on the left. In (B), the older model Foregger, two O_2 flowmeters are in the center, with flow controls offset from the scales! In (C), the modern Foregger has its O_2 flowmeter on the right, as will all future new US-made machines, following a recent agreement of US manufacturers.

Eger and colleagues[10] urged that the O_2 flowmeter be next to the flowmeter manifold outlet, to prevent escape of O_2 through a cracked or chipped flowmeter tube before it reached the outlet. Bishop's group[11] reported two such accidents due to this "fundamental fault in the design of the Boyle machine." When a hair crack developed in the cyclopropane Rotameter, without displacement of the broken parts, "the O_2 Rotameter, because of its position on the upstream side of the bank of Rotameters, will indicate a flow of O_2 which, in the event of a leak, will not reach the patient."[11]

Katz[12] and, 5 years later, Liew and Ganendran,[13] reported similar accidents with Drager Tiberius machines; again the O_2 flowmeter was on the left, farthest from the flowmeter manifold outlet. Liew and Ganendran had their problem 4 years after the manufacturing company had indicated that all its future flowmeter manifolds would be designed to deliver the O_2 to the manifold outlet despite any leak through another flowmeter.[14]

Low Flow, High Hazard.—The accidental use of low flows of O_2 when a high flow is intended is a built-in hazard whenever two O_2 flow controls are fitted.[15] Mazze[16] reports "death occurred in a 45-year-old man scheduled for hemorrhoidectomy. The anesthesia machine was equipped with two separate O_2 flowmeters, one calibrated in milliliters, the other in liters. The wrong O_2 flowmeter was used, resulting in 4 L of N_2O being delivered with 200 ml of O_2, rather than 2 L of O_2. Cardiovascular collapse occurred and the patient could not be resuscitated."

Solution.—Provide only one flow control valve for each gas! When low and high flows are required, two flowmeters placed in series are controlled by a single knob.

Separate Tube, Scale, and Float Hazards.—Some manufacturers insist that only by using plain flowmeter tubes and hand calibrating an individual scale for each tube can adequate accuracy be provided. As seven sizes of tube and three different weights of floats are used in differing combinations to provide the desired flow ranges, only a code letter and not the name of the gas is marked on the tube. So if the tubes and floats become separated from their scales, they may easily become mixed. It will not then be obvious that an error has been made unless volumetric checks are made. Though manufacturers caution their personnel not to remove more than one tube at a time, to err is human!

Malfunction of a New Anesthetic Machine.—Walts and Inglove[17] failed to produce satisfactory anesthesia with the salesman's "demonstrator," borrowed while their machine was being repaired. They found that, "by mistake, a small-bore rotameter tube had been used in place of the normally large-bore N_2O tube. No error had been made in the scale. So that, at an indicated flow of 5 L/min of N_2O, the flow was closer to 500 ml." Their problem was not unique, for Kelly and Gabel reported:

The Improperly Calibrated Flowmeter.[18]—"The 20 to 250 ml/min flowmeter to the Verni-Trol of one of our Ohio anesthesia machines was broken. The repairman installed a replacement which included *a new scale, tube and bobbin.* He did not check the flow calibration." When next used, the odor of halothane coming from the system was unexpectedly strong. "With the flowmeter set at 250 cc/min, the measured flow was approximately 1500 cc/min. This would have delivered roughly 6 times as much volatile anesthetic agent as the flowmeter indicated." Even though the repairman installed a complete flowmeter assembly—scale, tube, and float—a potentially lethal error occurred. This, then, is the true price of hand-calibrated accuracy with the present designs.

Chadwick[19] described, due to *transposition of rotameter tubes,* "the delivery of hypoxic anesthetic mixture to 2 patients undergoing general anesthesia for minor procedures. The anesthetic machine was a regularly maintained Ohio Unitrol® 'three-gas' table model." "The rotameter assembly was protected by a thick plastic shield, which also partly obscured the rotameter bobbins when these were at a position of zero gas flow. The machine was . . . used infrequently." It took two visits by the serviceman before the cause was discovered, "that, at a rotameter setting of 5 L/min of O_2, a volume of 400 ml was delivered. When the plastic cover was removed, it was observed that the rotameter tube was absent from the cyclopropane position; it was found to be in the O_2 (D) position." "In this machine, the rotameter tubes were not marked by etching on the glass but by scales fixed to the back of the rotameter panels, and the tubes are plain except for the code letter." Surely it is not too much to ask that this problem be eliminated once and for all

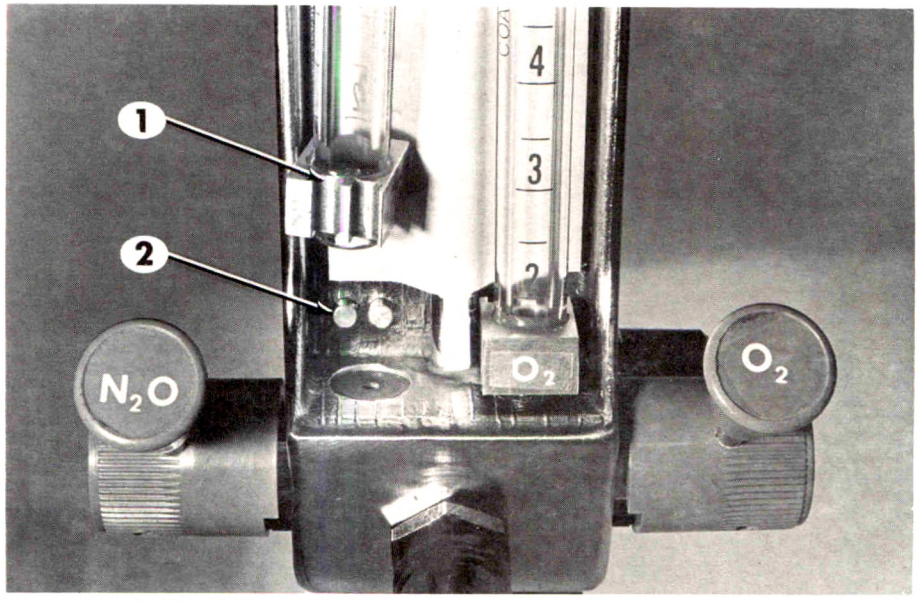


FIG 8. Prototype pin-index system for flowmeter tubes. (Developed by Porter Instrument Company, Hatfield, Pennsylvania, August 1974.) Prototype uses slots (1) machined into rear surface of metal base for flowmeter tube. When tube is correctly placed, pins (2) in flowmeter housing engage in slots and permit tube to be correctly seated. Should an error be made and an incorrect tube be placed in housing, pins do not correspond with slots and flowmeter cannot be assembled.

by using tubes with the scale and gas supplied etched onto them, or by use of a pin-index system for flowmeter tubes (fig 8). If, in addition, the balls or floats are all of the same size and weight, another chance for error is eliminated.

Touch Identification of O_2 Control Knobs.—Calverley[20] suggested and it has been agreed that the O_2 flow control knob shall have projections for positive touch identification. All the other flow control knobs will remain round (fig 9).

Prevention of Accidental Hypoxia.—The Matteo-Gissen-Lee gas-mixing system[21] and the Fraser Sweatman Quantiflex MDM System insure that not less than a preset minimum proportion of O_2 is delivered to the patient. Accidental hypoxia is thus prevented.

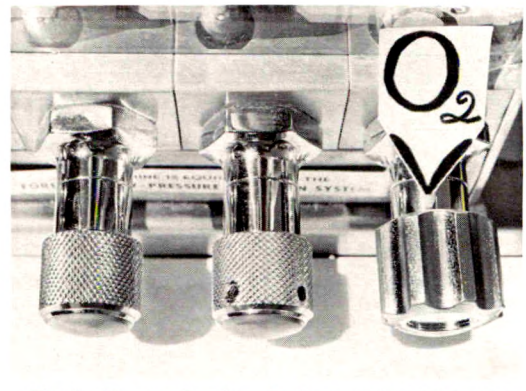


FIG 9. Proposed safety O_2 flow-control knob. Following Calverley's suggestion that the O_2 flow-control knob have projections to provide positive touch identification,[20] it is proposed that "to make the O_2 flow-control knob physically distinguishable, it shall have a characteristic profile" (shown here). "It may be arranged to project beyond the knobs controlling other gases in a bank of flowmeters. Its diameter shall be not less than the diameter of knobs controlling other gases. Other flow-control knobs shall be round." (ANSI-Z79 draft standard.)

CONCLUSIONS

There is little doubt that improvements in safety are urgently needed, but before they will be made, we anesthesiologists must indicate clearly that we will accept changes in the familiar apparatus we have used for years; the engineers would then be willing to make the changes, once they are sure other hazards are not thereby introduced. But first the firms' directors must be convinced that the disruption of the status quo is worthwhile. They will base their decisions on their sales department's report on whether their customers will welcome or at least accept the changes. Thus, in the final analysis, if enough anesthesiologists request, improvements will be introduced. Improvement awaits our initiative!

REFERENCES

1. Safar P, Galla SJ: Overdose with Ohio halothane vaporizer. Anesthesiology 23:715-716, 1962

2. Kopriva CJ, Lowenstein E: An anesthetic accident: cardiovascular collapse from liquid halothane delivery. Anesthesiology 30:246-247, 1969

3. Greenhow DE, Barth RL: Oxygen flushing delivers anesthetic vapor—a hazard with a new machine. Anesthesiology 38:409-410, 1973

4. Chun L, Karp M: Case history number 39: Accidental use of trichloroethylene (Trilene®, Trimar®) in a closed system. Anesth & Analg 43:740-743, 1964

5. Guzman CM, Cascorbi HF: An unusual hazard of methoxyflurane. Anesthesiology 36:305, 1972

6. Sweatman F: Foaming of methoxyflurane contaminated with silicone. Anesthesiology 38:407, 1973

7. Larsen ER: Foaming in halogenated anesthetics—the chemistry of modern inhalation anesthetics, Modern Inhalation Anesthetics. Edited by MB Chenoweth. New York, Springer-Verlag, 1972, p 29

8. Murray WJ, Zsigmond EK, Fleming P: Contamination of in-series vaporizers with halothane-methoxyflurane. Anesthesiology 38:487-490, 1973

9. Blum LL: Equipment design and "human" limitations. Anesthesiology 35:101-102, 1971

10. Eger EI II, Hylton RR, Irwin RH, et al: Anesthetic flow meter sequence—a cause for hypoxia. Anesthesiology 24:396-397, 1963

11. Bishop C, Levick CH, Hodgson C: A design fault in the Boyle apparatus. Brit J Anaesth 39: 908, 1967

12. Katz D: Recurring cyanosis of intermittent mechanical origin in anesthetized patient. Anesth & Analg 47:233-237, 1968

13. Liew PC, Gandendran A: Oxygen failure: a potential danger with air-flowmeters in anaesthetic machine with remote controlled needle valves. Brit J Anaesth 45:1165-1168, 1973

14. Katz D: Increasing the safety of anesthesia machines. I. Further modification of the Draeger machine. II. Considerations for the standardization of certain basic components. Anesth & Analg 48: 242-245, 1969

15. Eger EI II, Epstein RM: Hazards of anesthetic equipment. Anesthesiology 25:490-504, 1964

16. Mazze RI: Therapeutic misadventures with oxygen delivery systems: the need for continuous in-line oxygen monitors. Anesth & Analg 51:787-792, 1972

17. Walts LF, Inglove H: Malfunction of a new anesthetic machine. Anesthesiology 25:867, 1964

18. Kelly JM, Gabel RA: The improperly calibrated flowmeter—another hazard. Anesthesiology 33:467-468, 1970

19. Chadwick DA: Transposition of rotameter tubes. Anesthesiology 40:102, 1974

20. Calverley RK: A safety feature for anaesthetic machine-touch identification of oxygen flow control. Canad Anaesth Soc J 18:225-229, 1971

21. Matteo RS, Gissen A, Lee ASJ: Safety in the use of nitrous oxide. A modification of the standard anesthetic machine to eliminate sources of human error and system failure. Anesthesiology 31:361-369, 1969

FLAIL CHEST Intermittent mandatory ventilation (IMV) combined with PEEP significantly shortened the duration of artificial ventilation in the treament of flail chest. The duration of mechanical ventilatory support averaged 18.8 days using mechanical ventilation with zero end-expiratory pressure compared with 5.1 days in patients treated with IMV and PEEP. Duration of stay in the intensive care unit correlated directly with the type of ventilatory support (23 vs 8 days). The shorter ventilation times support the thesis that flail chest is not an orthopedic problem but one of pulmonary contusion. The combination of IMV and PEEP represents an improvement in the management of patients with flail chest. *(Cullen P, Modell JH, Kirby RR et al: Treatment of flail chest. Use of intermittent mandatory ventilation and positive end-expiratory pressure. Arch Surg 110:1099-1103, 1975)*

Cardiac Failure Associated with Hypocalcemia

J. KENNETH DENLINGER, MD*
MICHAEL L. NAHRWOLD, MD*
Hershey, Pennsylvania†

Rapid transfusion of citrated whole blood was associated with acute hypotension and a rising central venous pressure in a patient undergoing pelvic exenteration and hemipelvectomy. Evidence of cardiac failure was accompanied by a precipitous decrease in serum ionized calcium (Ca^{++}) concentration. When the rate of blood transfusion was slowed, arterial blood pressure returned to the control level and serum Ca^{++} increased.

SEVERE citrate-induced hypocalcemia [serum ionized calcium (Ca^{++}) concentration <0.5 mM/L] has been reported recently in pediatric patients receiving massive blood transfusions.[1] Hypocalcemia of this magnitude produces asystole in the isolated heart preparation[2] and may result in circulatory depression in anesthetized man.[3] Previous reports have not utilized direct measurements of serum Ca^{++} activity to substantiate the diagnosis of hypocalcemic cardiac failure in anesthetized man. In the following case history, clinical evidence of cardiac decompensation was accompanied by marked, but transient, hypocalcemia.

REPORT OF A CASE

A cachectic 27-year-old woman weighing 38.5 kg was admitted to the Clinical Center of the National Institutes of Health with the diagnosis of recurrent squamous-cell carcinoma of the cervix. Extension of her disease had produced partial right ureteral obstruction; however, renal function studies were within normal limits. There was no history of cardiopulmonary disease and her chest roentgenogram and ECG were normal. With the exception of hypoalbuminemia (serum albumin = 2.7 gm/100 ml and globulin = 3.9 gm/100 ml), indices of liver function were within normal limits. Other preoperative laboratory determinations included hgb, 10.4 gm/100 ml; serum Na^+, 133 mEq/L; Cl^-, 87 mEq/L; K^+, 2.7 mEq/L; CO_2 content, 32 mEq/L; total calcium, 4.65 mg/100 ml; phosphate, 4.8 mg/100 ml. It was thought that hypochloremic, hypokalemic alkalosis was the result of gastrointestinal loss, and that adequate potassium replacement could be achieved intraoperatively.

After premedication with 8 mg of morphine and 0.5 mg of scopolamine, anesthesia was induced with 200 mg of sodium thiopental intravenously and maintained with 1 to 2 percent enflurane in N_2O-O_2. Succinylcholine (50 mg) was given to facilitate tracheal intubation, and 9 mg of pancuronium was administered in divided doses, as needed, for muscle relaxation during the 13 hours required for total pelvic exenteration and right hemipelvectomy. Direct arterial and central venous pressures (CVP) were monitored by Statham strain

*Assistant Professor, Department of Anesthesia.

†The Milton S. Hershey Medical Center of the Pennsylvania State University, Hershey, Pennsylvania 17033.

Study conducted at the Department of Anesthesia, Clinical Center, National Institutes of Health, Bethesda, Maryland 20014.

Paper received: 3/31/75
Accepted for publication: 6/9/75

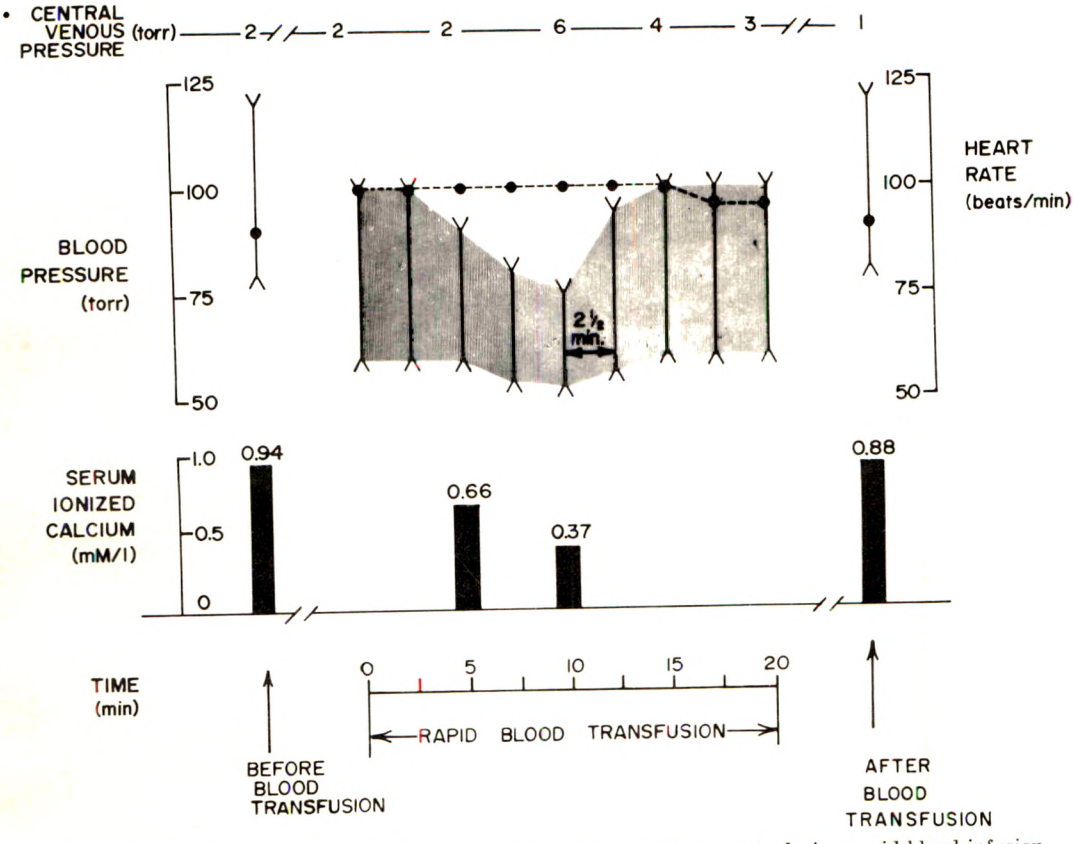


FIGURE. Hemodynamic changes and serum ionized calcium measurements during rapid blood infusion.

gauge. The ECG and esophageal temperature were also monitored continuously throughout the procedure.

After 3 hours of anesthesia, the patient's arterial blood pressure remained stable at 120/80 torr, heart rate was 90 beats/min, and CVP was 2 torr (figure). Esophageal temperature had fallen to 35.1 C; arterial blood-gas analysis revealed Pao_2, 179 torr; $Paco_2$, 39 torr; and pH, 7.47. Serum Ca^{++} concentration* was 0.94 mM/L (normal range = 0.96 to 1.20 mM/L). During the following 5-hour interval, 3500 ml of warmed citrated whole blood and 40 mEq of KCl were administered intravenously. Serum K^+ increased from 2.7 to 3.2 mEq/L.

Subsequently, an abrupt increase in blood loss necessitated transfusion under pressure via two large-bore cannulas at an estimated rate of 3 ml/kg body weight/min. CVP increased from 2 to 6 torr, while arterial blood pressure decreased from 90/60 to 75/50 torr over a 5-minute period. Heart rate was unchanged at 100 beats/min during this time and normal sinus rhythm was observed continuously. Serum Ca^{++} concentration, however, decreased from 0.66 to 0.37 mM/L (figure).

With achievement of hemostasis and reduction in transfusion rate, arterial blood pressure increased to 100/60 torr and CVP decreased to 4 torr. Arterial blood gases were Pao_2, 254 torr; $Paco_2$, 40 torr; pH, 7.50, and serum electrolyte determinations were Na^+, 140 mEq/L and K^+, 2.8 mEq/L. Although no exogenous Ca was administered, serum Ca^{++} increased to 0.88 mM/L when the rate of blood transfusion was slowed.

DISCUSSION

Although the documentation of a hypotensive event accompanied by hypocalcemia does not establish a causative relationship, etiologic factors such as surgical manipulation, anesthetic overdose, cardiac arrhythmias, hypoxia, hypercarbia, and acidosis can probably be excluded in this patient. Hypovolemia must be considered as a possible cause of hypotension associated with massive blood loss; however, this patient's

*Measurement with an Orion Research flow-through Ca electrode, Model 99-20.

CVP did not decrease at any time during the rapid blood replacement. Although CVP changes observed were small, hypotension in the face of a rising CVP is suggestive of cardiac inotropic failure. Such cardiac depression may result from hypocalcemia.

The administration of citrated whole blood at 150 ml/70 kg body weight/min during a 5-minute interval to normothermic, normocarbic, and normocalcemic anesthetized man results in a 41 percent decrease in serum Ca^{++} concentration.[4] Hypocalcemia of greater magnitude, as observed in our patient, is to be expected during multiple rapid transfusions.[5,6] Hypothermia and liver dysfunction may further accentuate the degree of hypocalcemia by decreasing the rate of metabolic clearance of exogenous citrate.[6]

The spontaneous recovery to normal blood pressure with achievement of hemostasis and decrease in transfusion rate is consistent with the hypothesis that the hypocalcemia of citrate toxicity is an extremely transient phenomenon, dependent on redistribution of citrate in the extracellular fluid space, hepatic metabolism of citrate, and rapid mobilization of Ca from bone.[4] In view of the extremely rapid changes in serum Ca^{++} which occur during rapid blood transfusion, it is not surprising that a safe and effective formula for maintenance of normocalcemia does not exist.

When direct measurements of serum Ca^{++} are unavailable, ECG monitoring of the QT interval is usually recommended to detect severe hypocalcemia. Although hypocalcemia does prolong the QT interval, we were unable to detect an increase in QT duration by observation of the oscilloscopic trace. Colletti's group[7] reported that the QoTc interval may be a more sensitive index of hypocalcemia than the QT interval. The QoT interval, derived from a written recording of the ECG, is measured from the origin of the Q wave to the onset of the T wave. Correction for the effect of heart rate is made by the formula: $\text{QoTc (sec)} = \text{QoT (sec)} / \sqrt{\text{RR interval (sec)}}$.

Unexplained cardiac decompensation accompanying rapid blood transfusion is best treated by prompt achievement of hemostasis and reduction in the rate of blood administration. When this is not possible and hypocalcemia is a consideration, small doses of IV $CaCl_2$ (3 mg/kg) may be useful to restore circulatory function.[8]

REFERENCES

1. Das JB, Eraklis AJ, Filler RM, et al: Serum ionic calcium: changes with large volume blood transfusions in the infant. J Pediat Surg 6:333-338, 1971

2. McLean FC, Hastings AB: A biological method for the estimation of calcium ion concentration. J Biol Chem 107:337-350, 1934

3. Bunker JP, Bendixen HH, Murphy AJ: Hemodynamic effects of intravenously administered sodium citrate. N Engl J Med 266:372-377, 1962

4. Denlinger JK, Nahrwold ML, Lecky JH, et al: Effect of citrated whole blood infusion rate on serum ionized calcium in anesthetized man. Abstracts of Scientific Papers, American Society of Anesthesiologists, 1974

5. Hinkle JE, Cooperman LH: Serum ionized calcium changes following citrated blood transfusion in anaesthetized man. Brit J Anaesth 43:1108-1112, 1971

6. Bunker JP, Stetson JB, Coe RC, et al: Citric acid intoxication. JAMA 157:1361-1367, 1955

7. Colletti RB, Pan MW, Smith EWP, et al: Detection of hypocalcemia in susceptible neonates, the QoTc interval. New Eng J Med 290:931-935, 1974

8. Denlinger JK, Kaplan JA, Lecky JH, et al: Cardiovascular effects of intravenously administered calcium in man during halothane anesthesia. Anesthesiology 42:390-397, 1975

Effect of Position (Semirecumbent Versus Supine) on Postoperative Oxygenation in Markedly Obese Subjects

ROBERT W. VAUGHAN, MD*
SPOMENKO BAUER, MD†
LESLIE WISE, MD‡
St. Louis, Missouri§

In 22 markedly obese, otherwise healthy, women studied postoperatively on each of days 1 through 3 after intra-abdominal operation, the effect of position change on arterial oxygenation was assessed. There was a statistically significant decrease in Pa_{O_2}, an increase in $A\text{-}aD_{O_2}$ and a simultaneous modest reduction in Pa_{CO_2} with the assumption of the supine position on postoperative days 1 and 2, but no positional difference demonstrable in any studied variable by day 3. This report suggests that during the first 48 hours after abdominal surgery in obese patients, assumption and maintenance of the semirecumbent posture is a valuable therapeutic modality to improve arterial oxygenation.

THE overall incidence of postoperative pulmonary complications, and hence hypoxemia, is affected by age, sex, duration of operation, body habitus, the existence of pre-existing pulmonary disease, and cigarette smoking.[1] Obese subjects undergoing abdominal surgery are recognized as being a particularly high-risk group in terms of postoperative pulmonary complications.[2] Recently we demonstrated that markedly obese subjects, after jejunoileal small bowel bypass, manifest significant hypoxemia during the first 4 postoperative days.[3] Since the maximum decrease in Pa_{O_2} in obese subjects occurred on postoperative days 1 or 2, any added positional effect on this already existent hypoxemia could further compromise oxygenation.

Our present study sought to identify, in a group of postoperative obese women, whether a change from the semirecumbent to the supine position would alter blood/gas exchange.

METHOD

Twenty-two morbidly obese nonsmoking women patients without clinical evidence of cardiopulmonary disease were studied postoperatively on each of days 1 through 3. Fourteen of these patients had been studied preoperatively. Informed consent was obtained from each unsedated patient preoperatively. The operative incisions (vertical midline) and surgical procedures (jejunoileal small bowel bypass, liver biopsy, and appendectomy) were identical for all patients. The overall mean duration of anesthesia was 186 minutes, with a SD of ± 23 minutes.

Samples of arterial blood were obtained

*Associate Professor of Anesthesiology.
†Anesthesia Resident, Barnes Hospital.
‡Associate Professor of Surgery.
§Departments of Anesthesiology and Surgery, Washington University School of Medicine, St. Louis, Missouri 63110.
Reprint requests to: Dr. Robert W. Vaughan, Department of Anesthesia, Arizona Medical Center, Tucson, Arizona 85724.
Paper received: 4/21/75
Accepted for publication: 6/2/75

preoperatively from 14 patients and postoperatively from all subjects, breathing room air for 15 to 20 minutes. The order of sampling positions was semirecumbent, then supine, each patient serving as her own control (semirecumbent). Sampling was anaerobic, from the radial artery by direct puncture, after infiltration of the skin with 0.5 percent lidocaine, or from an indwelling intra-arterial cannula. Arterial blood was collected in iced plastic syringes containing heparin, and analyzed for Po_2, Pco_2, and pH within 30 minutes of sampling, in our research laboratory. Appropriate corrections were made for changes produced by time and temperature.[4]

The alveolar-arterial O_2 tension difference (A-aDo_2) was calculated as follows:[5]

$$A\text{-}aDo_2 = PAo_2 - Pao_2 \text{ where } PAo_2 = PIo_2 - PAco_2 \left\{ FIo_2 + \frac{1 - FIo_2}{R} \right\};$$

PAo_2 = alveolar Po_2; $Paco_2$ = arterial Pco_2; PIo_2 = inspired Po_2; R = respiratory quotient.

Since Ellison and associates[6] reported that there was no measurable change in R as a result of routine surgical operations, we have assumed that R = 0.8 throughout.

Each arterial sample was taken at least 4 hours after any narcotic medication or respiratory therapy treatments. The arterial blood samples were obtained in the semirecumbent and supine positions each morning (usually between 0800 and 1000 hr); however, beginning in the recovery area and continuing throughout the postoperative period, all patients were maintained in the semirecumbent position.

Collected data was analyzed by analysis of variance within and among the two positions studied. Subsequently, the difference in means between the control (semirecumbent) and supine positions was submitted to Student's paired *t*-test.

RESULTS

This patient sample was young (mean age 33.8 yr) and markedly obese (mean of 140% in excess of ideal weight) (table 1). In the 14 patients studied preoperatively, no statistically significant difference in any blood-gas measurement was seen in the semirecumbent versus the supine position ($p > 0.05$). Semirecumbent Pao_2 was reduced (mean 74.7 ± 1.8 torr) when compared to nonobese patients matched for age;

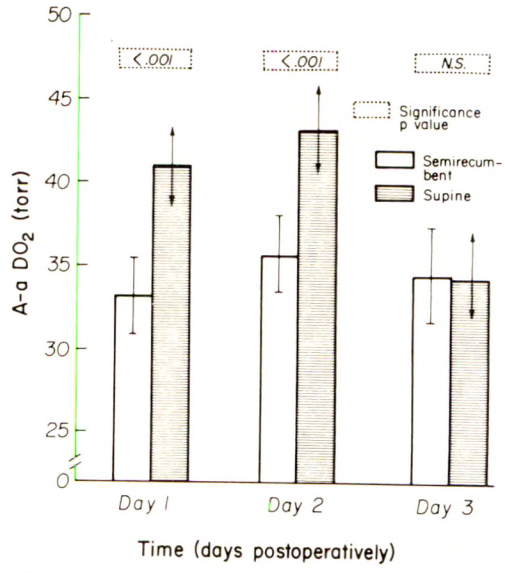


FIGURE. Alveolar-arterial O_2 tension difference (A-aDo_2) of 22 women patients in semirecumbent compared with supine position on each of postoperative days 1 through 3 (mean ± SE). On postoperative days 1 and 2, a change to supine resulted in a significantly greater increase ($p < 0.001$) in A-aDo_2. All values obtained with resting patient breathing room air.

assumption of the supine position actually improved oxygenation (78.3 ± 2.7 torr). Mean $Paco_2$ (semirecumbent) was 36.8 ± 0.6 torr, while the mean supine value was 35.1 ± 1 torr. Likewise, semirecumbent mean A-aDo_2 was 34.8 ± 1.8 torr, while supine the value decreased to 32.9 ± 2.8 torr.

Postoperatively, there was a statistically significant increase in A-aDo_2 between the semirecumbent and supine positions on postoperative days 1 and 2; no such difference was present by day 3 (table 2 and figure). Statistically significant positional differences in Pao_2 and $Paco_2$ were demonstrable on postoperative days 1 and 2 but not by the 3rd day (table 2).

No significant correlation was identifiable for the mean difference (supine-semirecumbent) in A-aDo_2 with age, weight/height ratio, or percent deviation from ideal weight on postoperative days 1 and 2.

DISCUSSION

No data are available relating the effect of changes in body position to A-aDo_2 in postoperative patients, either nonobese or obese. Since the postoperative obese patient would be at a particularly high risk if

TABLE 1

Physical Characteristics of 22 Adult Women Subjects

Case number	Age, yr	Height, cm	Body weight, kg	Deviation from ideal weight, %*	Weight, kg / Height, cm
1	27	162	154	192	0.95
2	27	173	156	153	0.90
3	37	150	116.4	146	0.78
4	33	175	128.6	103	0.73
5	31	168	125.5	116	0.75
6	24	168	155.5	168	0.93
7	38	165	141.8	154	0.86
8	36	163	128.6	137	0.79
9	38	165	190	240	1.15
10	39	159	150	188	0.94
11	34	175	142	124	0.81
12	30	178	178	173	1.00
13	52	163	118	117	0.73
14	27	160	104	97	0.65
15	47	163	160	195	0.98
16	31	177	125	97	0.71
17	25	178	154.1	136	0.87
18	29	170	131.4	120	0.77
19	42	165	125	124	0.76
20	26	171	119	99	0.70
21	42	170	128	114	0.75
22	29	164	104	86	0.63
Mean	33.8	167	138	140	0.82
SD	7.5	7	22.3	39.5	0.13

*Deviation from ideal weight $= \frac{\text{actual weight (kg)} - \text{ideal weight (kg)}}{\text{ideal weight (kg)}\dagger} \times 100$

†Ideal weight = determined from standard Metropolitan Life Insurance Company height/weight table[7] using midrange value of medium frame group at each height.

TABLE 2
Postoperative Differences in Blood-Gas Tensions Related to Change in Position (Semirecumbent to Supine)

Blood-gas variable	Semirecumbent		Supine		Mean difference (supine-semirecumbent)	Significance of difference (p value)
	Mean	SE	Mean	SE		
Postoperative day 1						
A-aDo_2	33.3	2.3	41.0	2.2	7.7	< 0.001
Pao_2	64.2	2.1	58.6	1.8	−5.6	< 0.001
$Paco_2$	39.1	0.8	37.4	0.7	−1.7	< 0.01
Postoperative day 2						
A-aDo_2	35.9	2.6	43.2	2.4	7.3	< 0.001
Pao_2	60.4	2.1	54.5	1.8	−5.9	< 0.001
$Paco_2$	40.0	0.9	38.9	0.9	−1.1	< 0.01
Postoperative day 3						
A-aDo_2	34.4	2.8	34.3	2.7	−0.1	NS*
Pao_2	61.4	2.7	61.5	2.4	0.1	NS
$Paco_2$	40.5	1.0	40.4	1.1	−0.1	NS

*NS = not statistically different by Student's t-test.
Values represent means of 22 adult women patients breathing room air. All units are torr.

changes in position altered gas exchange, we chose to study this group.

Tucker and Sieker[8] reported in nonobese patients the effect on lung volumes of a change from seated to recumbent position; significant decreases in all lung subdivisions except residual volume occurred. The expiratory reserve volume, in particular, was markedly reduced in the recumbent position.

Leblanc and coworkers[9] were the first to suggest the phenomenon of airway closure as a factor which might influence gas exchange with the change in posture. They pointed out that, while "closing volume" (lung volume at which airway closure started to occur) does not change substantially with posture, there is a decrease in functional residual capacity (FRC) in the supine position, thus increasing the chance of the closing volume falling within the breathing range. If this occurred, ventilation to affected regions would be impaired, thereby lowering the regional ventilation-to-perfusion ($\dot{V}a/\dot{Q}c$) ratios. This unevenness of ventilation would tend to promote arterial hypoxemia. Leblanc further reported in nonobese patients that the age at which closing volume began within the tidal range was about 65 years in the upright position and 44 years in the supine. Extrapolation of these data to our markedly obese patients is not possible.

Alexander's group[10] measured postoperative lung function to identify the mechanism of the observed hypoxemia. They demonstrated that all lung volumes were reduced following abdominal operation; the reductions were most severe after upper-abdominal operations. In their patients, there was a mean reduction of 28 percent in the FRC on postoperative day 1. They suggested that, after operation, the lung volume at which airways close [closing volume (CV)] might remain relatively unchanged while FRC decreased. Thus, there would be an increased likelihood of maldistribution of tidal volume (V_T), mismatching of ventilation with perfusion, and hypoxemia. Subsequently, they were able to show a significant correlation between the FRC-CV relationship and A-aDo_2.

Craig and colleagues[11] collected the only available data relating the effect of a change in posture (from seated to supine) on gas exchange. In 22 normal subjects, the change in A-aDo_2 with change in position as well as changes in the relationship of breathing level (FRC + V_T) to CV were evaluated. They found that the FRC decreased in the supine position, whereas CV was unchanged. The A-aDo_2 changes correlated directly

with the degree of impingement of CV on the breathing level. However, when subjects were grouped specifically according to weight, age, or smoking history, no effect of posture on gas exchange was demonstrable.

In contrast to Craig's study in nonoperated subjects, our postoperative results demonstrate that, in markedly obese women, position has a significant effect on the A-aDo_2. A possible pathophysiologic explanation for our findings is as follows:

(1) Postoperatively, abdominal muscle spasm accompanied the wound pain;

(2) Spasm of the expiratory muscles caused a rise in intrathoracic pressure leading to reduction in lung volumes, including FRC + V_T; gas exchange now took place at a lower lung volume;

(3) Subsequent assumption of the supine posture further accentuated the reduction in FRC, moving CV within the breathing range;

(4) This worsening of the $\dot{V}a/\dot{Q}c$ relationship led to a reduction in arterial oxygenation, thereby compromising overall 0_2 delivery.

It should be noted that there is another important factor in the morbidly obese. The marked weight of the abdomen can cause significant elevation of the diaphragm in the supine posture. We did not explore this factor in our study.

CONCLUSIONS

This study suggests that, in obese individuals, the assumption of the semierect posture is a valuable therapeutic modality to improve gas exchange after abdominal operation. One should be particularly cognizant of this postural effect on oxygenation in the first 48 postoperative hours. This precaution is probably most applicable to the older, markedly obese patient with a history of cigarette smoking. Prudence would dictate frequent assessment of arterial oxygenation as well as avoidance of the supine posture in these high-risk patients. Although this positional effect on postoperative oxygenation has not been demonstrated in nonobese subjects, one may suspect its occurence after thoracic and/or upper-abdominal procedures.

REFERENCES

1. Marshall BE, Wyche MQ Jr: Hypoxemia during and after anesthesia. Anesthesiology 37:178-209, 1972

2. Cahill JM: Respiratory problems in surgical patients. Amer J Surg 116:362-368, 1968

3. Vaughan RW, Engelhardt RC, Wise L: Postoperative hypoxemia in obese patients. Ann Surg 180:877-882, 1974

4. Kelman GR, Nunn JF: Nomograms for correction of blood Po_2, Pco_2, pH, and base excess for time and temperature. J Appl Physiol 21:1484-1490, 1966

5. Comroe JH Jr: Clinical physiology and pulmonary function tests, The Lung. Second edition. Chicago, Year Book Medical Publishers, 1965, pp 339-341

6. Ellison LT, Duke JF, Strickland GW, et al: Oxygen requirements in the early postoperative period (48 hours): ventilation and respiratory exchange. Ann Surg 163:559-563, 1966

7. Metropolitan Life Insurance Company table of desirable weights in adults, Documenta Geigy, Scientific Tables. Sixth edition. Philadelphia, Ciba Foundation, 1962, p 624

8. Tucker DH, Sieker HO: The effect of change in body position on lung volumes and intrapulmonary gas mixing in patients with obesity, heart failure, and emphysema. Amer Rev Resp Dis 82:787-791, 1960

9. Leblanc P, Ruff F, Milic-Emili J: Effects of age and body position on "airway closure" in man. J Appl Physiol 28:448-451, 1970

10. Alexander JI, Horton PW, Millar WT, et al: Lung volume changes in relation to airway closure in the postoperative period: a possible mechanism of postoperative hypoxemia (abstract). Brit J Anaesth 43:1196, 1971

11. Craig DB, Wahba WM, Don HF, et al: "Closing volume" and its relationship to gas exchange in seated and supine positions. J Appl Physiol 31:717-721, 1971

Hypnosis for Monitoring Intraoperative Spinal Cord Function

ALVIN H. CRAWFORD, MD*
CLYDE W. JONES, MD†
JERRY A. PERISHO, MD‡
JOHN A. HERRING, MD§
San Diego, California‖

In such procedures as the Harrington operation for idiopathic scoliosis, evaluation of spinal cord function is advisable immediately after the back is straightened. The authors have used hypnosis for this procedure, as an adjunct to anesthetic management. Patients are awakened on the table, given lower extremity tests, and are then reanesthetized. The incidence of postoperative pain and other discomfort is also reduced by hypnosis.

IN SEPTEMBER 1972, Pierre Stagnara presented a paper[1] on the advisability of checking spinal cord function during spinal surgery. As there is always a slight but real risk of paraplegia with instrumentation for correction of scoliosis, attention has been focused on the search for a method of evaluating spinal cord function during such procedures.[2,3]¶ The best and most obvious test of this function is voluntary motor power.[1]

Hypnosis.—At the Naval Regional Medical Center, San Diego, we employ Harrington instrumentation sparingly in the treatment of idiopathic scoliosis. By awakening the patient on the operating table during operation, evaluation can be accomplished much sooner than waiting until the patient is in the recovery room, over 1 hour later. We have found hypnosis useful for helping the patient cooperate in a series of intraoperative tests, moving only the desired extremities upon voice command.

¶Macewen GD: Personal communication.

Hypnosis, as described herein, is a temporary state of altered attention, induced by another person or by the subject himself, in which there is concentration upon a very narrow field. In this state, called the hypnotic trance, there is heightened suggestibility on the part of the subject, and the hypnotist can direct the subject's concentration to achieve alterations of awareness, muscular relaxation, memory, and fatigue. Sensory and motor changes can be induced and removed during this hypnotic state.[4]

The use of hypnosis in surgical anesthesia has been well established. It may be used as the sole anesthetic technic or as a supplement thereto. Posthypnotic suggestion is useful for the management of pain, muscle spasm, nausea and vomiting following operation. It can also be used to assist the patient in deep breathing and coughing following abdominal and thoracic surgical procedures.

*Head, Pediatric Orthopedic Division, Department of Orthopedics.
†Chairman, Department of Anesthesiology.
‡Former Staff Anesthesiologist.
§Staff Orthopedist.
‖Naval Regional Medical Center, San Diego, California 92134.

The opinions or assertions in this paper are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

Paper received: 3/31/75
Accepted for publication: 6/19/75

•Untoward effects of hypnosis are a matter of controversy, but include the danger of precipitating or worsening a psychiatric illness, of masking symptoms of physical or mental disease, and of excessive dependency on the part of the patient.[5]

Hypnosis is used only as an adjunct to the anesthetic management of our patients; we do not place excessive dependence on the hypnotic aspects but regard the entire management as a unit. In conjunction with the Department of Anesthesiology, the Department of Pediatric Orthopedics set up the following protocol.

Protocol.—All patients scheduled to undergo operation for idiopathic scoliosis are admitted to the hospital 2 weeks before operation and placed in Cotrel's traction. About 1 week before operation, the anesthesiologist gives the patient a complete explanation of the reasons for the intraoperative tests, the part hypnosis plays in the total scheme, and what hypnosis is. Particular emphasis is given to explaining away the myths[6] and superstitions regarding hypnosis, stressing that the patient will also receive conventional chemical anesthesia, will feel no pain during the operation, and will probably not even recall the intraoperative awakening. A test of "hypnotizability," such as the eye-roll test,[6] is given, and in the ensuing week, the patient is placed in a hypnotic trance several times, the number of times depending on the patient's response to hypnosis and degree of cooperation.

Patients, 15 female and 3 male, ranged in age from 12 to 22, 16 being in the 12 to 16 age group, and one each ages 19 and 22. Their ages and their motivation for a successful outcome of this procedure resulted in excellent cooperation by all patients, irrespective of their degree of suggestibility. About two thirds were good to moderate hypnotic subjects. Because hynosis was not the sole technic, this was not of crucial importance.

The verbal technic was used for induction of hypnosis, achieving hypersuggestibility by a state of muscular relaxation. The onset and depth of trance were facilitated by posthypnotic suggestion and repetition of suggestions. The thrust of the suggestions during the trance state was directed at the simulation of the intraoperative scene and the tests of toe and ankle flexion and extension to be performed on command.

During the hypnotic trance, the entire procedure is outlined, with an effort to describe the situation in the operating room at the time of testing. The suggestions include that they will have no fear on the day of operation, either before, during, or after the procedure. The idea that they have control over their skeletal muscles is suggested and demonstrated. The part played by muscle relaxation in the reduction of postoperative pain is particularly stressed. It is always suggested that, while discomfort will be less, analgesics will be available if needed.

Patients are told that when they awaken, they will open their eyes and nod to show that they understand. They will not move on the table except the feet and legs, as instructed by the anesthesiologist. The reasons for their position, the function of mechanical ventilation, of the endotracheal tube, and of monitoring and IV equipment are explained. The sessions are continued one or more times a day until the hypnotist-anesthesiologist considers that results are satisfactory.

Intraoperative Management.—On the day of operation, the patient is premedicated with diazepam and a small dose of narcotic. Lactated Ringer's solution is then administered by a #14 IV cannula. Induction is with Innovar® and diazepam or sodium thiopental IV. A nondepolarizing relaxant is administered and, after spraying the larynx and trachea, the trachea is intubated by direct laryngoscopy.

Anesthesia is maintained by balanced technic, using N_2O-O_2, IV meperidine, diazepam, or thiopental and d-tubocurarine or pancuronium bromide, with controlled ventilation. By judicious use of small doses of meperidine and relaxant intermittently, reversal of these drugs is not necessary before testing.

Intraoperative monitoring includes precordial and esophageal stethoscope and temperature, ECG, and Doppler blood pressure determinations, central venous pressure, arterial blood gases, and sometimes bladder indwelling catheterization.

When instrumentation is completed, the patient is awakened by turning off the N_2O and ventilating the patient with 100 percent O_2. A 30-minute warning signal allows the anesthesiologist to "wind down" for the test. Instillation of 4 percent lidocaine by catheter into the trachea via the endotracheal tube at this time reduces the chance

of reaction to the tube, and sometimes return to spontaneous ventilation facilitates awakening. The patient blinks when awake and, understanding instructions, carries out the voluntary tests; when it is demonstrated to the surgeon's satisfaction that the cord is intact, anesthesia is resumed and the surgical procedure is completed.

RESULTS

We have now successfully monitored 18 patients using this technic and have experienced no failures. Three of the 18 patients represented the deepest trance group, as demonstrated by the induction of profound limb anesthesia, amnesia, and negative hallucination. Four staff anesthesiologists and 5 residents participated. Scoliosis has not been severe enough (39 to 109°) to require tremendous intraoperative correction, and no instrumentation has been used in any of our congenital cases.

These procedures have taken ± 5 to 6 hours of anesthesia time, the intraoperative tests being performed about 1 hour before the end. No patient has reported recall, nor has any patient manifested fear or panic during the tests. Two patients moved the arms slightly but caused no problem. No attempts have been made to induce recall of the test by hypnosis, since it is felt that this would serve no useful purpose.

Postoperative Management.—It has been noted that these patients required less pain medication in the immediate (2 to 3 days) postoperative period, but the statistical significance cannot be documented at this time and remains only a clinical impression. Postoperatively, the hypnotic trance is continued by some of the anesthesiologists to decrease immediate discomfort, bladder spasm, and nausea, as well as to teach the patient autohypnosis, a valuable adjunct to the tolerance of postinstrumentation appliances and immobilization.

CONCLUSION

It is our feeling that, far from being a mystique, hypnosis is a refined and sophisticated method of having patients move their extremities in a controlled fashion while undergoing surgical procedures and anesthesia, where indicated, instead of purposeless flailing. We plan to continue it as outlined, though not to attempt its use as the total anesthetic in this extensive surgical procedure.

REFERENCES

1. Vauzelle C, Stagnara P, Jouvinoux P: Functional monitoring of spinal cord activity during spinal surgery. Clin Orthop 93:173-178, 1973

2. Goldstein LA: Current and developing aspects in management of scoliosis. New York J Med 72: 2977-2992, 1972

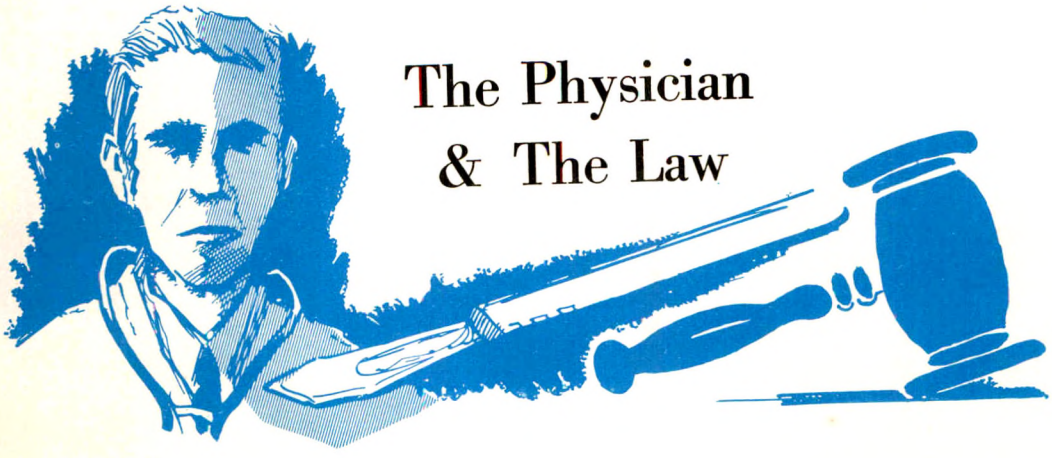
3. Keim HA, Hilal SK: Spinal angiography in scoliosis patients. J Bone Joint Surg 53A:904-912, 1971

4. Medical use of hypnosis—Report of the Council of Mental Health. JAMA 168:186-189, 1958

5. West LJ, Deckert GH: Dangers of hypnosis. JAMA 192:9-12, 1965

6. Morris K, Spiegel H, Rockey EE: Hypnosis in surgery: exploding the myths. The Surgical Team 3:30-37, 1974

METHEMOGLOBINEMIA A patient being treated for an acute myocardial infarction and receiving sodium nitroprusside to reduce left ventricular afterload developed cyanosis unrelated to hypoxia. After 4 days of sodium nitroprusside treatment (total dose 321 mg) cyanosis of the nail beds was noted and the methemoglobin level was 16%. The authors speculate that their patient had acquired methemoglobinemia, and in the absence of exposure to other oxidizing drugs or foodstuffs, that nitroprusside or one of its metabolic products was responsible for the symptoms observed. *(Bower PJ, Peterson JN: Methemoglobinemia after sodium nitroprusside therapy. NEJM 293:865, 1975)*



The Physician & The Law

$1,237,500 Settlement for Brain Damage During Appendectomy

THREE physicians and a hospital settled a malpractice suit brought in a California trial court for a total of $1,237,500.

Claiming that the physicians and the hospital were negligent in the performance of an appendectomy on her son, the mother brought an action against them. She claimed that they failed to drain his stomach before the operation, failed to pass an endotracheal tube to assure adequacy of his air supply, and failed to monitor his heart and respiration during the operation with a precordial stethoscope.

The patient had trouble breathing on his own after surgery, and the anesthesiologist injected Prostigmin to counteract the supposed effect of curare. The patient immediately vomited and aspirated a large quantity of the material.

His heart stopped abruptly after he vomited, but he was resuscitated and left in a recovery room. The recovery room nurse was not advised that he had suffered a cardiac arrest.

He never awakened from the anesthesia and suffered seizures from permanent brain damage. At the time of trial, he was unable to speak or see and had no bowel or bladder control.

Two medical experts in anesthesiology testified that the standard of care required the use of an endotracheal tube and a precordial stethoscope. They also said that Prostigmin should not have been given without something to avoid the vomiting side-effect. One of the experts said that curare should not have been used and that blood gas tests and X-rays should have been ordered.

The anesthesiologist being sued admitted that use of an endotracheal tube was accepted practice but said that he had not

Reprinted with permission from THE CITATION published by the Law Division of the American Medical Association.

used one in order to save time. He claimed that the history of ingestion given by the patient's mother was inaccurate and was the reason for the complication.

The operating physician testified that he did not order blood gas tests because the patient's color had returned to normal just after the vomiting. The recovery room nurse testified that she made the decision to discontinue oxygen when he opened his eyes. She also decided whether to give Demerol for restlessness and when to discharge him from the recovery room.

The physician who diagnosed the patient's appendicitis and brought the operating physician into the case settled for $50,000, half to the patient and the other half to the mother to dismiss a second suit brought against him. The hospital settled before trial for $87,500.

At the start of the third week of trial the anesthesiologist settled for $1,000,000 and the operating surgeon for $100,000. The money was placed in trust, with any balance left at the patient's death to be returned to the insurance carriers for the physicians and hospital.—*Fernandez v. Salinas Valley Memorial Hospital* (Cal.Super.Ct., Monterey Co., Docket No. 69306, Oct. 28, 1974)

CORRECTION

The first paragraph under discussion in the article "Comparison of Methotrimeprazine and Meperidine as Components of Balanced Anesthesia" which appeared in the November-December issue page 754, should read:

As with other CNS depressants, the preliminary administration of MTM and meperidine significantly decreased the induction dose of thiopental. In this respect, 0.1 mg/kg of droperidol,[15] 1.5 mg/kg of meperidine, and 0.5 mg/kg of MTM are about equipotent and permit 60 percent reduction in the induction dose of thiopental.

Hemodynamic Effects of Morphine During and Early After Cardiac Operations

EMERSON A. MOFFITT, MD*
SAIT TARHAN, MD
RAMON RODRIGUEZ, MD
DONALD A. BARNHORST, MD
JAMES R. PLUTH, MD

Hemodynamics and blood gases were measured before and 15 minutes after small (10 mg/70 kg) doses of intravenously administered morphine in two groups of patients having open heart surgery. In one group, the study was undertaken after median sternotomy but before perfusion. The other group had been in the intensive care unit for approximately 1 hour. No changes were found in either group in cardiac index, atrial pressures, arterial pressure, or blood gas variables. However, mean systemic vascular resistance decreased from 41.5 to 35.4 after morphine was given postoperatively. Hence, hemodynamically, morphine is a safe drug if given in small doses for pain relief and sedation early after open heart surgery.

PREVIOUSLY we investigated the hemodynamic effects of small doses (up to 12 mg) of morphine given intravenously 1 hour after open heart operation in 32 patients.[1] With cardiac index relatively low at that time (average 2.2 liters/min per m^2), no significant changes were found in mean index, arterial and right atrial pressures, heart rate, or peripheral resistance. Because the effects were unpredictable in individual patients, we extended the study and included measurements of left atrial pressure. This paper reports the effects of morphine given intravenously (10 mg/70 kg) in 7 additional patients studied postoperatively and 10 investigated during surgery (but before perfusion).

METHODS

Sixteen of the 17 patients were men. Ages ranged from 41 to 73 years and all but one had New York Heart Association class III or IV heart disease (Table 1). Aortic valves were replaced in 11, and 6 received vein grafts for coronary artery disease. Anesthesia utilized nitrous oxide, oxygen, curare, and small concentrations of halothane. No opiates or other drugs were given, except for the morphine for the study. Perfusions employed the Bentley bubble oxygenator with flows of 2.0 to 2.2 liters/min per m^2 at temperatures of 30 to 32° C.

After induction of anesthesia, a Teflon catheter was inserted percutaneously into

Departments of Anesthesiology and Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901.

This investigation was supported in part by Research Grant GM-14919 from the National Institutes of Health, Public Health Service.

*Present address: Professor and Head, Department of Anaesthesia, Dalhousie University, Halifax, Nova Scotia, Canada B3H 2Y9.

Paper received: 7/7/75
Accepted for publication: 8/14/75

TABLE 1
Patient Data

Group	Mean age (yr)	Mean wt (kg)	Mean surface area (m^2)	New York Heart Association class		Operation	Average dose of morphine (mg)
				Class no.	No. pts		
Intraoperative study (10 patients)	55.3	69.7	1.83	III	8	Aortic valve replacement—6, coronary vein graft—4	10
				IV	2		
Postoperative study (7 patients)	61.1	74.3	1.86	II	1	Aortic valve replacement—5, coronary vein graft—2	10.6
				III	3		
				IV	3		

the femoral artery and advanced to the thoracic aorta. Ventilation was controlled at F_{IO_2} of 0.4 to 0.5. After median sternotomy but before arterial and venous cannulations, the studies were carried out. Arterial and left and right atrial pressures and heart rate were measured and recorded, and arterial blood was sampled for blood gas determinations. Duplicate dye dilution curves were obtained utilizing transit of indocyanine green from left atrium to thoracic aorta. Then, morphine sulfate (10 mg/70 kg) was given slowly intravenously. After 15 minutes (without cardiac manipulation) all measurements were repeated. Blood gases were determined by electrodes at 37° C.

The postoperative studies were accomplished in the manner previously reported,[1] approximately 1 hour after the patients entered the intensive care unit. The sequence included sampling arterial blood, measuring and recording right and left atrial and arterial pressures and heart rate, obtaining duplicate dye curves, and then giving morphine intravenously (10 mg/70 kg). All measurements were repeated after 15 minutes. No other drugs were given before or during the study, but the chest-tube drainage was replaced volume-for-volume. Assisted respiration via endotracheal tube (F_{IO_2} 0.4 to 0.5) was employed. Mean arterial pressure was assumed to be the sum of the diastolic pressure and one-third of the pulse pressure. Systemic vascular resistance was considered to be the ratio of the difference in mean arterial and left atrial pressures to the cardiac index. The data were analyzed using Student's t test for paired and unpaired data, and each variable was compared before and 15 minutes after administration of morphine. ($P<0.05$ was selected as the level of significance.)

RESULTS

Measurements of atrial and arterial pressures, systemic resistance, and cardiac index in the intraoperative study are listed in Figure 1 and blood gases and heart rate in Figure 2. In intraoperative studies (before perfusion), no significant changes other than changes in heart rate occurred after administration of morphine.

In the patients receiving morphine postoperatively in the intensive care unit, lowered systemic vascular resistance was the only significant change ($P<0.02$) after administration of morphine (Figures 3 and 4).

Comparison of the two patient groups by analysis of unpaired data revealed mean arterial pressure and $Paco_2$ to be lower intraoperatively than postoperatively, both before and after administration of morphine. Both before and after morphine administration, mean right atrial pressure was

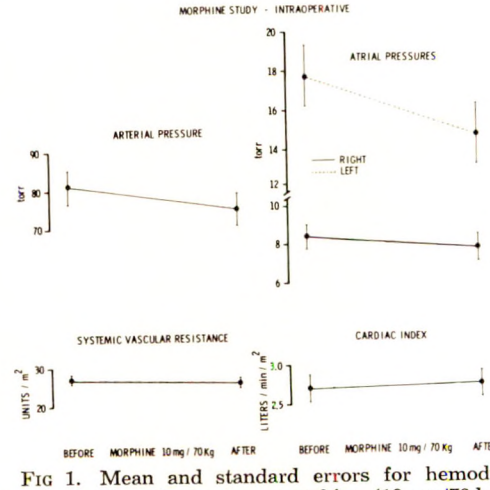


FIG 1. Mean and standard errors for hemodynamics in 10 patients given morphine (10 mg/70 kg) after median sternotomy but before perfusion.

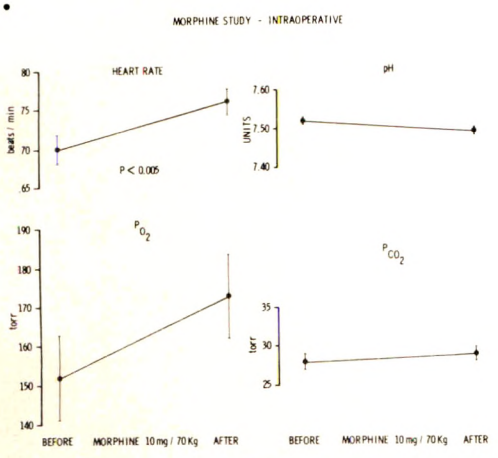


FIG 2. Heart rate and blood gas variables in 10 patients given morphine intraoperatively.

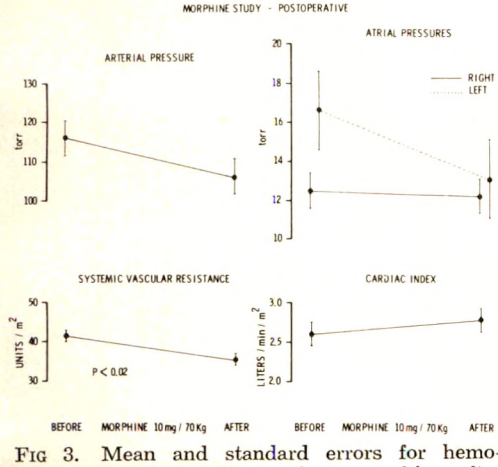


FIG 3. Mean and standard errors for hemodynamics in seven patients given morphine after 1 hour in intensive care unit.

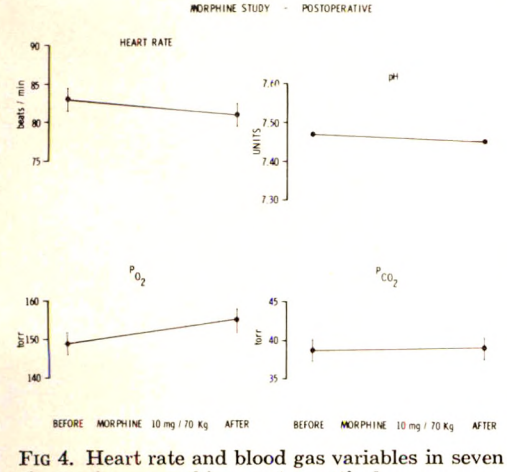


FIG 4. Heart rate and blood gas variables in seven patients given morphine postoperatively.

lower intraoperatively than postoperatively, whereas mean systemic vascular resistance before administration of morphine was lower in the intraoperative study than in the postoperative study.

COMMENT

After the appearance of the first report of the use of morphine intravenously for anesthetizing cardiac surgical patients,[2] the doses prescribed were increased to high levels (8 to 10 mg/kg).[3,4] As disadvantages became obvious,[4-7] the usual total dose prescribed was decreased to a more conservative level (1 to 2 mg/kg).[5]

Popularity of the morphine technique has prompted considerable investigation of the effects of morphine on the heart and circulation and other body systems. Stoelting and Gibbs[8] studied the effect of morphine in the most pertinent model, the cardiac patient. In their patients having aortic valve or coronary vein graft operations, a dose of 1 mg/kg significantly increased the cardiac index and lowered the systemic resistance and arterial pressure. When nitrous oxide, the agent most frequently used with morphine, was added, both cardiac index and arterial pressure decreased.

The lack of significant effect of 10 mg of morphine administered intravenously 1 hour after surgery to a 70 kg patient confirmed previous results.[1] However, this time a significant decrease in arteriolar resistance occurred. The present group of patients did have lower resistance (mean 41.5 U m^2) before the morphine was given than did those in the earlier study (mean 52.6 U m^2), but the earlier patients were severely vasoconstricted and had a lower cardiac index (mean 2.14 liters/min per m^2). Arterial and right atrial pressures and heart rates did not differ between groups. Again, we attribute the lack of effect to the small dose (compared to amounts given for anesthesia) of morphine.

Although cardiac index and left atrial pressures were the same, several differences in conditions were present between the patients studied during surgery and those studied after surgery. Arterial pressure, right atrial pressure, and systemic vascular resistance were lower intraoperatively. Lowered pressure, due to diminished vascular resistance, was likely caused by anesthesia. Another difference was the lower $Paco_2$

during anesthesia due to intentional hyperventilation. However, even on these different hemodynamics before perfusion, the small dose (10 mg) of morphine produced no significant changes.

We also measured left atrial pressure because it is a more direct determinant of cardiac output than right atrial pressure. Neither intraoperatively nor postoperatively did left atrial pressure change after administration of morphine, a finding consistent with the unchanged cardiac outputs. Therefore, hemodynamically, morphine is a safe drug if given for pain relief and sedation in small doses early after open heart surgery.

REFERENCES

1. Morrison JD, Moffitt EA, Danielson GK, et al: Circulatory effects of morphine early after open-heart surgery. J Thorac Cardiovasc Surg 63:890-895, 1972

2. Lowenstein E, Hallowell P, Levine FH, et al: Cardiovascular response to large doses of intravenous morphine in man. N Engl J Med 281:1389-1393, 1969

3. Hasbrouck JD: Morphine anesthesia for open-heart surgery. Ann Thorac Surg 10:364-368, 1970

4. Mannheimer WH: The use of morphine and intravenous alcohol in the anesthetic management of open heart surgery. South Med J 64:1125-1127, 1971

5. Lowenstein E: Morphine "anesthesia": a perspective (editorial). Anesthesiology 35:563-565, 1971

6. Stanley TH, Gray NH, Stanford W, et al: The effects of high-dose morphine on fluid and blood requirements in open-heart operations. Anesthesiology 38:536-541, 1971

7. Stanley TH, Gray NH, Isern-Amaral JH, et al: Comparison of blood requirements during morphine and halothane anesthesia for open-heart surgery. Anesthesiology 41:34-38, 1974

8. Stoelting RK, Gibbs PS: Hemodynamic effects of morphine and morphine-nitrous oxide in valvular heart disease and coronary-artery disease. Anesthesiology 38:45-52, 1973

ABSTINENCE FROM SMOKING Cigarette smokers have a higher incidence of pulmonary complications postoperatively than a comparable group of nonsmokers. The authors tested the hypothesis that abstinence from smoking for a short time preoperatively was beneficial. Pulmonary function tests were performed before and for 7 days after cessation of smoking in 5 chronic smokers (mean 14 pack/day/year). All had normal spirometric measurements (FVC, FEV_1) and maximum voluntary ventilation before abstinence from smoking. In contrast, all had a significant reduction in flow at 25 per cent of the vital capacity (FEV_{25}) indicating significant small airway disease. Cessation of smoking for 7 days produced no change in any of these tests. The authors conclude that advice to "stop smoking for even 2 to 3 days before surgery" is inadequate preoperative preparation for the patient with obstructive lung disease. Chest physiotherapy, bronchodilators and breathing exercises must also be employed. *(Chodoff P, Margand PMS, Knowles CL: Short term abstinence from smoking: Its place in preoperative preparation. Crit Care Med 3:131-133, 1975)*

The Pulmonary Absorption-Excretion Volume Effect

HERBERT RACKOW, MD*
ERNEST SALANITRE, MD†
New York, New York‡

An *in-vitro* experiment demonstrated the concentration effect of N_2O (3% versus 75%) during elimination and during uptake. Other pulmonary absorption-excretion phenomena also occur simultaneously, as paired events during uptake and then during elimination: diffusion hyperoxia and diffusion anoxia; alveolar concentration of CO_2, and alveolar dilution of CO_2. These clinical phenomena, as well as the second gas effect, are all related, and the pulmonary absorption-excretion volume is found to depend in part on the type of ventilation: volume controlled, pressure controlled, or spontaneous respiration.

THE uptake or elimination of N_2O in anesthetic concentrations involves the exchange of significant volumes of this gas between lungs and blood.[1-3] Absorption or excretion of these relatively large volumes of N_2O has been associated with changes in concentrations of certain alveolar gases. These changes were reported by various investigators as different clinical phenomena, depending upon which alveolar gas was considered and whether uptake or elimination of N_2O was studied: diffusion anoxia,[2] diffusion hyperoxia,[4,5] alveolar dilution,[4] concentration effect,[6] and second gas effect.[7-9]

There is a common mechanism for each of these phenomena:[4]

1. During uptake, absorption of N_2O draws in an additional inspired tidal volume and/or reduces the alveolar volume.

2. During elimination, excretion of N_2O does the reverse, decreasing the inspired tidal volume and/or expanding the alveolar volume.

Since it is the same volume of N_2O and the same mechanism that causes all these clinical conditions, each can be regarded as a different aspect of one effect. Therefore, the phenomena must all occur together and as paired events, one due to absorption of N_2O during induction and two, its counterpart due to excretion of N_2O during recovery. Thus, diffusion anoxia (during recovery) has, as its counterpart, diffusion hyperoxia (during induction), and alveolar dilution of CO_2 (during recovery) is paired with alveolar concentration of CO_2 (during induction). The concentration effect, and its associated second gas effect, have only been reported during uptake. They should be found during recovery also.

Recently, Eger[10] stated that "recovery differs from induction by the absence of the concentration effect," basing this on two factors: uptake draws N_2O from an infinite reservoir,§ while the elimination reservoir formed by the blood is finite, and uptake shrinks the alveolar gas volume while elimination does not shrink the blood volume.

Our understanding of the basic mechanism is different: Uptake draws a finite

§Changes in tidal volume are discussed below.

*Professor of Anesthesiology.

†Professor of Clinical Anesthesiology.

‡Department of Anesthesiology, College of Physicians and Surgeons, Columbia University and the Anesthesiology Service of Presbyterian Hospital, New York, New York 10032.

This study was supported in part by NIH Grant GM 09069.

Paper received: 4/21/75
Accepted for publication: 8/5/75

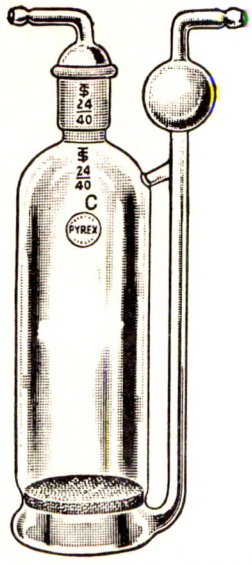


FIG 1. Gas-washing cylinder used for the "body" of equilibration studies.

volume of N_2O from an infinite reservoir, and elimination dumps this finite volume into an infinite sink. The reciprocal effects on tidal volumes and alveolar volumes have already been referred to.

In order to help resolve the disagreement, we have studied the concentration effect in a simple *in vitro* experiment during *both* uptake and elimination.

MATERIALS AND METHODS

The apparatus used for the *in-vitro* study was a gas-washing cylinder with a sintered glass disk at the bottom (fig 1).* The "body" was 600 ml of water which almost filled the cylinder, leaving a gas space of about 25 ml at the top where the standard taper 24/40 joint was located. A constant-volume Bournes pediatric ventilator or a constant-volume Harvard perfusion pump forced "breaths" of gas (100% O_2 or 3% N_2O, balance O_2, or 75% N_2O, balance O_2) through the sintered glass disk. The gas was dispersed into fine mist-like bubbles that agitated the water and emerged into the air space at the top. There the gas was sampled by a sampling pump previously described[11] and passed through an infrared N_2O analyzer.†

*B6040, Scientific Glass, Bloomfield, New Jersey.

†Beckman Instruments, LB 2 analyzer, modified by removing the linearizer. This permitted increased gain so that low and high concentrations could be analyzed without further adjustment of the instrument.

The movement of gas in the system was: tank source (100% O_2, 3% N_2O or 75% N_2O) → rubber breathing bag (fitted with a light pop off valve) → constant-volume ventilator → "body" of 600 ml H_2O → air space above H_2O → sampling pump → infrared N_2O analyzer.

The sequence in each study was:

1. 100% O_2 for 15 minutes.
2. 3% N_2O for uptake until F_E/F_I‡ reached 0.99. Ventilation continued for 15 minutes longer.
3. 100% O_2 for elimination of 3% N_2O, until a concentration of 0.05% N_2O was reached.
4. 75% N_2O for uptake until F_E/F_I reached 0.99. Ventilation continued for 15 minutes longer.
5. 100% O_2 for elimination of 75% N_2O. This constituted one study. Five studies were done.

At frequent periods during each study, inspiratory gas was sampled at the rubber breathing bag and analyzed for N_2O concentration, and the N_2O analyzer was calibrated against known N_2O concentrations delivered from previously analyzed, premixed tanks. Equilibration curves were constructed by converting "expiratory" N_2O concentrations to F_E/F_I ratios and plotting against time.

The water was kept at 0 C. The tidal volume and frequency were constant for any one study but varied among the studies from 1.5 ml to 20 ml and from 25 to 50 times per minute.

RESULTS

All 5 studies, each consisting of uptake and elimination of 3% and then 75% N_2O, showed a faster approach to equilibrium for the 75% N_2O for both uptake and elimination. In all studies, there was a greater difference between the 3% and 75% N_2O during uptake than during elimination. Figure 2 shows a representative study.

DISCUSSION

The *in-vitro* studies were designed to determine whether the concentration effect occurred for both uptake *and* elimination. There were no physiologic parameters of

‡F_E/F_I = "expiratory" concentration of N_2O/inspiratory concentration.

cardiac output or tissue perfusions, etc, that could vary and influence the results. The model consisted of 2 compartments in series: a "body" of 600 ml of water and an air space of 25 ml for sampling. The larger size of the water compartment weighted the sample to reflect predominantly the changes in the water compartment more than changes in the air space.

The N_2O absorbed from the bubbles during uptake of 3% N_2O or added to the bubbles during elimination of 3% N_2O could not have changed the bubble volume significantly. This was the control uptake-and-elimination experiment.

Absorption of 75% N_2O, however, would reduce the *size* of each bubble from that of the control (the 3% N_2O bubble), and in so doing, would increase the concentration of the N_2O (and O_2) remaining in the bubble. This in turn would increase the tension gradient and cause more N_2O to be absorbed. This is the concentration effect during uptake (and also diffusion hyperoxia) with constant volume ventilation.

During elimination, excretion of N_2O into the bubbles would increase the *size* of the bubble over that of control. This would decrease the concentration of N_2O (and O_2) in the bubble, compared to what the concentration would have been had the size remained essentially unchanged (as with 3% N_2O). This decrease in concentration would increase the tension gradient and increase further elimination of N_2O. Thus, at constant inspired volume, there should be a faster elimination as well as faster uptake, i.e., a concentration effect should occur during both recovery and induction.

It is important that both the 3% and 75% uptake studies reach equilibrium, or the same relative position from equilibrium, before the elimination studies begin; otherwise a comparison of the elimination curves is meaningless. An equal time for each uptake cannot be considered for this purpose because the 75% uptake is faster than the 3% uptake.

In all 5 *in-vitro* studies, the 75% equilibration curves approached the equilibrium limit ahead of the 3% curves for both uptake and elimination (fig 2); thus, a concentration effect is seen to exist for both induction and recovery. This lends support to our interpretation of the dual mechanisms of shrinkage and expansion which cause all

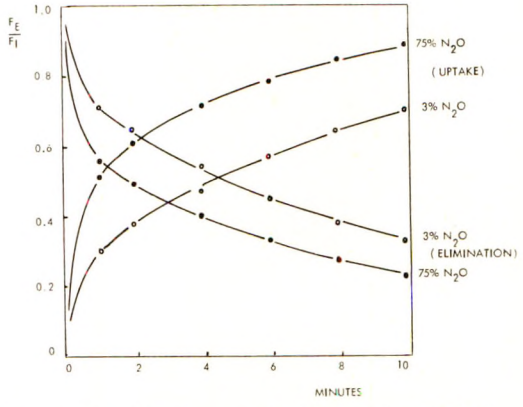


FIG 2. Equilibration of 3% N_2O and 75% N_2O during uptake and during elimination.

pulmonary absorption-excretion volume phenomena.[4]

The 3% uptake and elimination curves are virtual mirror images; this follows classic theory. However, the 75% uptake and elimination curves are *not* mirror images, the 75% uptake equilibration curve always showing a greater concentration effect than does the corresponding 75% elimination curve (fig 2). This is explained as follows:

Assume a water/air ratio of 1 and that a breath of 100 ml volume of 75% N_2O equilibrates with a 100 ml volume of water. In the first breath of uptake, 37.5 ml of N_2O should dissolve in the water, leaving 37.5 ml remaining in the air. The N_2O concentration in the water should theoretically rise to 37.5% and in the air should theoretically fall from 75% to 37.5% (75 ml of N_2O reduced to 37.5 ml/100 ml original breath volume). With the absorption volume effect reducing the total air volume, the concentration of N_2O in the air would be higher than 37.5% (37.5 ml N_2O/62.5 ml total breath volume) and the water/air ratio would not be 1. Continued absorption occurs until the ratio does become 1, at which time the concentration would be 50 ml of N_2O/100 ml H_2O and 25 ml N_2O/50 ml gas mixture (O_2 + N_2O). It is this further absorption that increases the rate of uptake for high N_2O concentrations, amounting to 12.5 ml of N_2O over and above that which would have been dissolved had no shrinkage of gas volume taken place.

After many "breaths" of 75% N_2O, at equilibrium, the 100 ml of water would contain 75 ml of N_2O. In the first breath of elimination, 37.5 ml of N_2O should theoretically enter the breath volume, leaving 37.5 ml of N_2O behind in the water. The

concentration of N_2O in the air should theoretically be 37.5% (37.5 ml N_2O/100 ml original breath volume). With the expansion effect, the volume of N_2O in the air would be 37.5 ml in a total air volume of 137.5 ml. The partition ratio would be more than 1, and further elimination would occur until the ratio reached 1. At this time, the concentration of N_2O would be approximately 31 ml of N_2O/100 ml H_2O and 44 ml of N_2O/144 ml of total air volume. This represents 6.5 ml more of N_2O than would have been excreted had no expansion of gas volume occurred. This is the concentration effect during elimination. It is less of an effect than during uptake.*

The Concentration Effect With Other Types of Ventilation.—In the present study, a volume-controlled ventilator was used and the entire effect of absorption and then excretion of N_2O was first to reduce and then to expand the bubble volume. The same effect on the alveolar volume should occur *in vivo*.

However, with a pressure-limited ventilator and with spontaneous respiration *in vivo*, other effects occur, due to changes in the tidal volume. During inspiration, absorption of N_2O draws in an equal, additional volume of inspired air. This results in a normal end-inspiratory volume of the lung and a normal end-inspiratory alveolar P_{CO_2}, despite the increased inspired volume. In effect, the increased inspired tidal volume contracts down (by absorption of N_2O) to a normal tidal volume. This increases the concentration of each gas in the *inspired* volume.

During expiration, continued absorption of N_2O reduces the alveolar volume and raises the concentration of all *alveolar gases*, O_2, CO_2, N_2O, and halothane, if present. With spontaneous respiration, the physiologic response to the increase in P_{CO_2} would be to increase (further) the next inspired breath; in effect, absorption of N_2O during both inspiration *and* expiration results in the added inspired volume. This causes a normal expired volume and a normal P_{CO_2}.

Elimination is the reverse; the excretion of N_2O during inspiration reduces the normal inspired tidal volume, dilutes the reduced inspired tidal volume, and also dilutes the alveolar volume (table).

Although the concentration effect with a volume-controlled ventilator resulted in a faster approach to equilibrium during recovery, with a pressure-controlled ventilator or with spontaneous respiration, it may result in a *slower* approach. *During uptake*, with pressure-controlled and spontaneous respiration, both the concentrating effect and the increased inspired tidal volume *speed* uptake. *During recovery*, however, although there is a diluting effect which should speed elimination, there is also a diminished inspired tidal volume which must tend to slow elimination, since it represents a form of hypoventilation.

The difference between uptake and elimination, with ventilation other than constant-volume ventilation, occurs, because during uptake, absorption *augments* the *inspired* volume and diminishes the expired volume, while during elimination, excretion *diminishes* the *inspired* volume and augments the expired volume. The alveolar-capillary tension gradient which determines the rate of absorption and excretion is a function of the inspired volume, not the expired volume. Only with a volume-controlled ventilator, is inspired volume kept constant.

Let us assume for the purposes of this discussion that with spontaneous respiration, during elimination, the inspired tidal volume is so reduced that the exhaled tidal volume and P_{CO_2} are kept constant (table). Since the expired tidal volumes are the same for elimination of both high and low concentrations of N_2O, and the inspired tidal volumes are smaller for elimination of high concentrations, there must be an overall slowing of elimination of high concentrations of N_2O compared to low concentrations. The larger the volume of excreted N_2O per breath, the greater the effect.

During recovery with a pressure-limited ventilator, just as with spontaneous respiration, there is a diluting effect, which speeds recovery, and a reduced inspired tidal volume, which slows recovery. However, the inspired tidal volume is not diminished as much as with spontaneous respiration (table), and there should be less slowing. The equilibration curve during recovery from

*An additional factor, not present *in vivo*, was that a decrease in bubble size during uptake increases the surface:volume ratio. During uptake, this may favor diffusion, if diffusion was a limiting factor under our conditions. The reverse during elimination may decrease diffusion. This may have further reduced the magnitude of the concentration effect during elimination. We thank Dr. W. Perl, New Jersey Medical School, Newark, for this suggestion.

TABLE

Effect of Type of Ventilation on Volumes Entering and Leaving Alveoli

	Inspiration			Expiration
	Volume inspired	Absorption or Elimination of N_2O		Volume expired
Control period 1,2,3. (all types of respiration)	$V_{I,c}$	None	None	$V_{E,c}$
		Concentrating Effect (absorption of N_2O_I and N_2O_E)		
Uptake period 1. Constant-volume respirator	$V_{I,c}$	$-N_2O_I$	$-N_2O_E$	$V_{E,c} - N_2O_I - N_2O_E$
2. Constant-pressure respirator	$V_{I,c} + V_{I,n2oi}$	$-N_2O_I$	$-N_2O_E$	$V_{E,c} - N_2O_E$
3. Spontaneous respiration	$V_{I,c}$ $V_{I,(n2oi + n2oe)}$	$-N_2O_I$	$-N_2O_E$	$V_{E,c}$
		Diluting Effect (elimination of N_2O_I and N_2O_E)		
Elimination period 1. Constant-volume respirator	$V_{I,c}$	$+N_2O_I$	$+N_2O_E$	$V_{E,c} + N_2O_I + N_2O_E$
2. Constant-pressure respirator	$V_{I,c} - V_{I,n2oi}$	$+N_2O_I$	$+N_2O_E$	$V_{E,c} + N_2O_E$
3. Spontaneous respiration	$V_{I,c} - V_{I,(n2oi + n2oe)}$	$+N_2O_I$	$+N_2O_E$	$V_{E,c}$

$V_{I,c}$ = control inspired tidal volume.
$V_{E,c}$ = control expired tidal volume.
$+ V_{I,n2oi}$ = additional inspired tidal volume equal to volume of N_2O absorbed during inspiration
$+ V_{I,(n2oi + n2oe)}$ = additional inspired tidal volume equal to volume of N_2O absorbed during inspiration and expiration
$- V_{I,n2oi}$ = reduced inspired tidal volume equal to volume of N_2O excreted during inspiration
$- V_{I,c\ n2oi + n2oe)}$ = reduced inspired tidal volume equal to volume of N_2O excreted during inspiration and expiration
$\pm N_2O_I$ = volume of N_2O absorbed (−) or excreted (+) during inspiration
$\pm N_2O_E$ = volume of N_2O absorbed (−) or excreted (+) during expiration

75% N_2O, using constant-pressure ventilation, should fall between that of the constant-volume ventilator and that of spontaneous respiration; but based on theory alone, we are unable to place it relative to the curve for 3% N_2O, i.e., without a volume effect.

If all parameters of uptake and elimination were held constant, the uptake equilibration curve of alveolar concentration with time would be the mirror image of the elimination curve, and independent of concentration.[12] However, because of the pulmonary absorption-excretion volume effect, ventilation is not a parameter but an additional variable. Classic theory of uptake holds only as the pulmonary absorption-excretion volume approaches zero,[6] that is, for low concentrations of soluble gases or all concentrations of relatively insoluble gases. For high concentrations of N_2O, the pulmonary absorption-excretion volume modifies the respiratory pattern of the different types of ventilation during uptake and elimination (table).

During uptake, spontaneous respiration has the largest inspired and expired volume compared to other types of ventilation; it should have the fastest rate of pulmonary equilibration and the maximum pulmonary absorption-excretion volume effects on O_2, N_2O, etc. As the constant-volume ventilator has the smallest inspired and expired volumes, it should have the slowest rate of equilibration. During elimination, the reverse occurs. As the pulmonary absorption-excretion volume approaches zero, the various modifications on all respiratory volumes, due to different types of ventilation, also approach zero.

CONCLUSIONS

The net pulmonary absorption or excretion of a relatively large volume of gas causes volume changes in the lung. This occurs during the first few minutes of uptake or elimination of N_2O in anesthetic concentrations and results in: (1) a concentrating effect during uptake and a diluting effect during elimination and, (2) changes in the inspired tidal volume, the end-inspiratory volume, the expired tidal volume and/or the end-expiratory volume. The type of ventilation, volume-controlled, pressure-controlled, or spontaneous respiration, has an effect on the pulmonary absorption-excretion volume. The clinical phenomena, diffusion anoxia, diffusion hyperoxia, the concentration effect, the second gas effect, and alveolar concentration and dilution of CO_2, are all related and all occur as simultaneous paired events during uptake and elimination with anesthetic concentrations of N_2O.

REFERENCES

1. Severinghaus JW: Rate of uptake of nitrous oxide. J Clin Invest 33:1183-1189, 1954

2. Fink BR: Diffusion anoxia. Anesthesiology 16:511-519, 1955

3. Sheffer L, Steffenson JL, Birch AA: Nitrous-oxide-induced diffusion hypoxia in patients breathing spontaneously. Anesthesiology 37:436-439, 1972

4. Rackow H, Salanitre E, Frumin MJ: Dilution of alveolar gases during nitrous oxide anesthesia in man. J Appl Physiol 16:723-729, 1961

5. Heller ML, Watson TR: The role of preliminary oxygenation prior to induction with high nitrous oxide mixtures. Polarographic Pao_2 studies, Anesthesiology 23:219-230, 1962

6. Eger EI II: Effect of inspired anesthetic concentration on the rate of rise of alveolar concentrations. Anesthesiology 24:153-157, 1963

7. Epstein RM, Rackow H, Salanitre E, et al: Influence of the concentration effect on uptake of anesthetic mixtures: the second gas effect. Anesthesiology 25:364-371, 1964

8. Stoelting RK, Eger EI II: An additional explanation for the second gas effect. A concentrating effect. Anesthesiology 30:273-277, 1969

9. Kitahata LM, Taub A, Conte AJ: The effect of N_2O on alveolar CO_2 tension: a second gas effect. Anesthesiology 35:607-611, 1971

10. Eger EI II: Anesthetic Uptake and Action. Baltimore, The Williams & Wilkins Company, 1974, p 231

11. Rackow H, Salanitre E: The pulmonary equilibration of cyclopropane in infants and children. Br J Anaesth 46:35-42, 1974

12. Salanitre E, Rackow H, Greene LT, et al: Uptake and excretion of subanesthetic concentrations of nitrous oxide in man. Anesthesiology 23: 814-822, 1962

Laryngeal Stenosis in Acromegaly: A Possible Cause of Airway Difficulties Associated with Anesthesia

SHAKEELA Z. HASSAN, MD*
GREGORY J. MATZ, MD†
A. M. LAWRENCE, MD, PhD‡
PHILLIP A. COLLINS, MD§
Chicago, Illinois‖

After difficult intubation in an acromegalic patient was encountered, 7 additional acromegalic patients were studied by measuring the cricoid width and anteroposterior diameter. Cricoid width and anteroposterior diameter were generally found to be narrower than in a group of normal patients. Such narrowing may explain airway problems encountered in acromegalic surgical patients.

ACROMEGALY was first described as a disease entity by Pierre Marie[1] in 1886. Laryngeal and pharyngeal involvement in acromegaly and the clinical entity of dyspnea in association with acromegaly were first recorded in 1896 by Chappell,[2] who described a patient dying of respiratory failure. At autopsy, a note was made of marked hypertrophy of the laryngeal cartilages, thickening and enlargement of the tonsils and other soft tissues, and a very narrow opening between the vocal cords.

In 1918, Chevalier Jackson[3] reported 4 patients with acromegaly and laryngeal morbidity, one of whom required a tracheostomy for what was described as severe airway obstruction caused by overgrowth of soft tissue and cartilages. Because of this experience, Jackson advocated careful examination of the larynx in all cases of acromegaly, as serious stenosis of the larynx could lead to dyspnea and even asphyxia due to airway obstruction.

Grotting and Pemberton[4] reported that fixation of the vocal cords could be seen in acromegaly. They proposed that this was presumably due to selective growth of the tracheal cartilages, with stretching of the recurrent laryngeal nerve and subsequent cord paralysis. Siegler[5] described a 35-year-old acromegalic woman with dyspnea and inspiratory stridor, presumably caused by bilateral vocal cord paralysis. Other authors[6,7] have also reported laryngeal stenosis and airway difficulties associated with acromegaly, attributing these problems to the enlarged tongue and generally thickened tissues of the upper airway. No mention of laryngeal measurements is made in any of these reports.

Only one report[7] has attested to difficulties encountered during routine intubation

*Associate Professor, Department of Anesthesiology.
†Associate Professor, Department of Surgery (Otolaryngology).
‡Professor, Department of Medicine (Endocrinology).
§Associate Professor, Department of Radiology.
‖University of Chicago, Chicago, Illinois 60637.

Paper received: 4/30/75
Accepted for publication: 6/9/75

of acromegalic patients. Recently, one of us encountered difficulty during intubation of such a patient. This led us to measure 7 acromegalic patients, as determined by tomography and indirect laryngoscopy, and to compare these measurements with those of normal men and women of relatively similar age and weight.

These observations emphasize the importance of precautionary preoperative assessment of airway adequacy in acromegalic patients about to undergo surgical anesthesia. Such attention may well avoid serious morbidity during intubation, anesthesia, and recovery.

MATERIALS AND METHODS

Case Report.—A 43-year-old man weighing 88 kg was admitted for elective herniorrhaphy. Because of a mildly abnormal preoperative cardiogram, evaluation by the medical service was requested and the presumptive diagnosis (subsequently confirmed) of acromegaly was suggested. No preoperative otolaryngoscopic examination was performed. Clearance for operation was given and the following morning, 75 mg of meperidine, 10 mg of diazepam, and 0.4 mg of atropine were given as premedication at 0700 hr.

The patient was transported to the operating room where the anesthesia team started parental fluids and attached monitoring terminals. At 0815 hr, 300 mg of sodium thiopental was administered IV, followed by 80 mg of succinylcholine, and endotracheal intubation was approached using standard laryngoscopic technics. Adequate visualization of the laryngeal orifice was not difficult, yet a size 8.5 and 8 mm Murphy tubes were too large to be inserted. The patient's spontaneous respiratory effort had returned and anesthesia was continued with a face mask, using halothane-N_2O-O_2 and assisted ventilation.

On external examination, laryngeal size appeared quite large, yet the opening between the vocal cords appeared very narrow. During attempts at intubation, occasional premature ventricular contractions were encountered. Subsequently, sinus rhythm was resumed throughout the intraoperative course. No persisting ECG abnormality was seen in the postoperative period or at the time of discharge from the hospital, 4 days later.

Seven acromegalic patients, ranging from 26 to 66 years in age, were chosen for laryngoscopic studies. All had received conventional cobalt radiation therapy in the past. With two exceptions, all had had marked lowering of elevated growth hormone levels toward or into the normal range, but clinical signs of smoldering disease were considered present in all but one. Each patient underwent indirect laryngoscopic examination, with careful attention to size of the tongue, size and symmetry of laryngeal cartilages, and mobility of vocal cords. X-ray examination of the larynx consisted of frontal biplanar tomograms and routine lateral soft-tissue films. The anteroposterior diameter and width of the cricoid cartilage were measured (figs 1, 2, and 3).

RESULTS

Unfortunately, laryngeal measurements of our first-reported acromegalic surgical patient were not made. However, of the 7 additional patients, all had coarse, thickened voices and enlarged tongues. No patient had either unilateral or bilateral vocal cord paralysis. The length of the larynx appeared normal on indirect examination but the cricoid width measurements generally showed a significant narrowing when compared with nonacromegalic patients (table). The anteroposterior diameter was not narrow and conformed to data reported from normals by Maue and Dickson.[8] No apparent differerences in the thyroid cartilage or in the cricothyroid angle were noted.

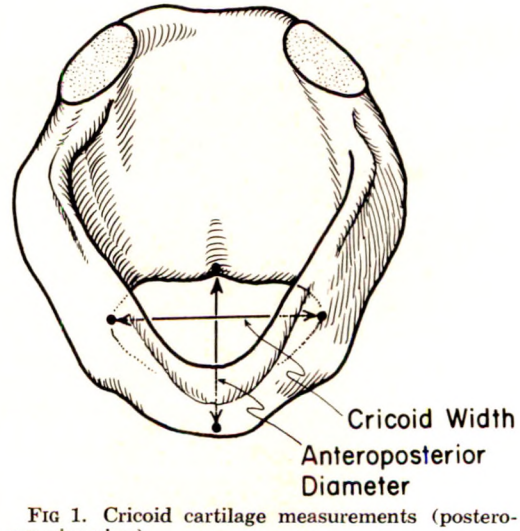


FIG 1. Cricoid cartilage measurements (posterosuperior view).

FIG 2. Plain soft tissue view of larynx in lateral projection.

TABLE

Cricoid Measurements in Acromegalic (A) and in Normal (N) Patients

Age	Sex	Cricoid width, mm	Anteroposterior diameter, mm
26A	M	12	20
18N	M	20	20
46A	F	13	16
59N	F	18	19
50A	F	10	19
39N	M	18	20
50A	M	16	16
50N	M	16	22
53A	F	15	21.5
71N	F	15	23
63A	M	15	22
65N	M	21	22
66A	M	15	24
75N	M	15	25

FIG 3. Anteroposterior tomogram of larynx.

DISCUSSION

Previous reports[2,4,5,9] have suggested that airway obstructive symptoms in patients with acromegaly may be due to enlarged or thickened soft tissues of the nasopharynx and larynx or associated vocal cord paralysis. Our group of 7 patients did not show strikingly thickened soft tissues of the larynx and none demonstrated recurrent laryngeal nerve palsy. However, increased hoarseness in a number of these patients could be due to some increased thickening of the vocal cords.

The tongue, although thickened in all, in itself would not appear to render intubation particularly difficult or materially lead to symptoms of dyspnea. The combination of significant decrease in the width of the cricoid arch associated with an enlarged tongue could nevertheless hamper a smooth intubation and lead to associated problems during the surgical procedure and in the postanesthetic period. Actual visualization of the vocal cords may be extraordinarily difficult.[9]

Intubation may be thwarted because of generalized thickening of laryngeal and pharyngeal structures, while anesthesia problems may arise because of the large nose, hypertrophied and obstructing nasal cartilages, prognathism and spreading teeth, and an unusually large tongue. The enlarged nose and fleshy facial soft tissues may effectively prevent adequate fitting of an anesthetic mask.

Recommendations for avoiding some of these problems[7] have included:

1. Preoperatively, the upper airway should be examined carefully, and accurate assessment made as to anticipated intra- or postoperative difficulties.

2. Intraoperatively, if difficulties in maintaining an adequate airway are anticipated, awake oral or nasal intubation under topical anesthesia or preoperative tracheostomy should be seriously considered.

3. Jackson's "sniffing" position,[10] with profound relaxation, is best for tracheal intubation.

4. Close postoperative observations of these patients will help prevent further airway complications.

REFERENCES

1. Marie P: Sur deux cas d'acromégalie: hypertrophie singulière, non congénitale, des extremités supérieures, inférieures et céphaliques. Rev Med (Paris) 6:297, 1886

2. Chappell WF: A case of acromegaly with laryngeal and pharyngeal symptoms. J Laryng 10: 142, 1896

3. Jackson C: Acromegaly of the larynx. JAMA 71:1787-1789, 1918

4. Grotting J, Pemberton J: Fixation of vocal cords in acromegaly. Arch Otolaryng 52:608-617, 1950

5. Siegler J: Acromegaly associated with laryngeal obstruction. J Laryng 66:620-621, 1952

6. Bhatia ML, Misra SC, Prakash J: Laryngeal manifestations in acromegaly. J Laryng 80:412-417, 1966

7. Kitahata LM: Airway difficulties associated with anaesthesia in acromegaly. Brit J Anaesth 43:1187-1190, 1971

8. Maue WM, Dickson DR: Cartilages and ligaments of the adult human larynx. Arch Otolaryng 94:432-439, 1971

9. Burn JM: Airway difficulties associated with anaesthesia in acromegaly. Brit J Anaesth 44:413-414, 1972

10. Jackson CL: Bronchoscopy, Esophagoscopy and Gastroscopy. Third edition. Philadelphia, WB Saunders Company, 1934, p 85

THE EFFECT OF PROLONGED BREATHING OF O_2 IN HIGH CONCENTRATION ON THE RESPIRATORY SYSTEM: EXPERIMENTAL INVESTIGATIONS. Although no attempt was made to extrapolate results from dogs to man, statistically impressive data were derived from a study of 17 dogs (7.5 to 30 kg) investigated to answer 3 major questions: (1) What is the effect (in dogs) of breathing 100% O_2 at 1 atm (600 torr) for up to 48 hours? (2) Can controlled respiration alter the action of prolonged O_2 breathing in high concentrations? (3) What, if any, pulmonary damage results from breathing? Assessment of the cardiorespiratory system was based on an analysis of indices determining (1) respiratory mechanics, (2) ventilation:perfusion relationships, (3) gas-exchange values, (4) O_2 transport and utilization in tissues, (5) morphologic lung changes. The author concludes: (1) All dogs showed pulmonary damage after 30 hours, changes beginning by the 12th hour and appearing during spontaneous as well as mechanical O_2 ventilation. (2) Respiratory rate, A: a ratio, and pulmonary shunting increased; lung compliance decreased; CO_2 excretion was impaired. (3) Pulmonary morphology showed extensive atelectasis and exudative reaction. (4) Mechanical respiration increased the O_2-induced damage. (5) Long-term quiet breathing of O_2 also disturbed the $\dot{V}/\dot{Q}$ ratio. (6) If long-term high concentrations of O_2 must be administered, Pa_{O_2} should not be permitted to exceed 100 torr, as dysplasia bronchopulmonalis is likely to result even earlier in man than in dogs. *(Szreter. Anaesth Resusc Intensive Ther 1:305-324, 1973.)*

Caudal Analgesia for Quadruplet Delivery

EZZAT ABOULEISH, MD*

During the period January 1969 to November 1974, in a total of 39,800 deliveries, there were two sets of quadruplets. Both parturients had been taking ovulation-inducing drugs. Maternal problems were distended abdomen and heavy uterus, causing supine hypotension and lordosis; toxemia of pregnancy; increased possibility of hemorrhage before, during and/or after delivery; edema of the back; mental depression. The fetal problems were prematurity; intrauterine growth retardation; increased possibility of transfusion syndrome and prolapsed cord; increased obstetric manipulation.

An adequate number of obstetricians, pediatricians, anesthesiologists, and nurses, necessary equipment, and blood and blood components should be available. Early hospitalization is necessary. Close observation of the patient before, during, and after delivery is essential. The patient should stay on her side throughout labor. General anesthesia may add to fetal depression and increase the possibility of uterine atony. Spinal or lumbar epidural anesthesia may be difficult because of the associated lordosis and back edema. Caudal block allowed intrauterine manipulation, provided adequate analgesia, permitted high F_{IO_2} administration, and did not interfere with voluntary bearing down when required.

ANESTHESIA for management of patients with multifetal gestation has a vital role in the welfare of mother and neonates, yet in extensive literature on the obstetric management of four or more fetuses, anesthetic problems and management is not discussed in detail.[1-19]

At Magee-Womens Hospital from January 1, 1969 to November 30, 1974, in a total of 39,800 deliveries, two sets of quadruplets were born. Both mothers delivered their quadruplets within the last year period, and both had taken ovulation-inducing drugs. The use of such drugs increases the incidence of multifetal gestations by increasing the frequency of multiple simultaneous ovulations. In several series in which these drugs had been used thirty to 50 percent of women who conceived had multiple gestations, including quintuplets, sextuplets, and septuplets.[17] The anesthesiologist will encounter cases of multifetal gestations with increasing frequency; therefore, he should be aware of the problems involved.

CASE REPORTS

Case 1.—A 33-year-old Caucasian woman was treated for primary infertility and oligo-ovulation due to polycystic ovarian syndrome. The first fertility drug used was clomiphene citrate (Clomid®), without success. The administration of human post-menopausal gonadotropins (Pergonal®) for a 3-month period was followed by conception of quadruplets. The patient's pregnancy course was uneventful. At about 30 weeks gestation she was admitted to the hospital and arrangements were made to have adequate personnel and equipment for anesthesia, delivery, and neonatal resuscitation available at any time.

At 0800 on November 10, 1973, at 35 weeks gestation, the patient was admitted to the labor suite with irregular contractions. Her height was 170 cm and her weight at this time was 75 kg. The cervix was 2 to 3 cm dilated and the head of the first fetus was at −2 station. BP was 120/80, pulse rate was 68, temperature was

*Associate Professor of Clinical Anesthesiology, University of Pittsburgh School of Medicine; Director of Obstetric Anesthesia, Magee-Womens Hospital, Pittsburgh, Pennsylvania 15213.

Paper received: 4/28/75
Accepted for publication: 5/19/75

36.7 C, and urinalysis was negative for albumin and dextrose. There was marked abdominal distention and lordosis but landmarks at the caudal hiatus were easily identified. She was relatively comfortable and did not require medication.

At 1530, she started to feel uncomfortable; the cervix was 8 to 9 cm dilated with the fetal head at +1 station and she was transferred to the Delivery Room, where two obstetricians, four neonatologists with necessary equipment for resuscitation and incubators, one anesthesiologist, two nurse anesthetists, and obstetric nurses were waiting. A 20-gauge Teflon epidural catheter* was inserted without difficulty into the caudal canal in the left semiprone position. To reduce the total dose of local anesthetic and to reach an adequate height of segmental block, a large segment of the epidural catheter, 12.5 cm, was left in the caudal canal to reach a high level.[20]

After a negative aspiration test for blood or cerebrospinal fluid, a test dose of 4 ml of 0.5 percent bupivacaine was injected. Five minutes later, a therapeutic dose of 19 ml of the same solution was slowly injected. The patient remained on her left side for 10 minutes, then gently turned to the other side where she remained until delivery time.

She was given 600 ml of 5 percent dextrose in water through an IV cannula within 15 minutes after the test dose, was closely monitored, and given O_2 by transparent plastic face mask. Within 20 minutes after the test dose, analgesia was adequate and extending on both sides to T-10 and vital signs remained stable. When the cervix was fully dilated, she was able to bear down while still on her side.

At 1630, the patient was transferred to the delivery table, put in lithotomy position with uterus displaced to the left, and O_2 administration was continued. Delivery of the quadruplets was uneventful and all were viable. Apgar ratings and other data are summarized in table 1. The interval between delivery of the first and last fetuses was only 19 minutes. The placentas were manually removed and the uterus was contracting well.

At 1720, the patient was transferred to the Recovery Room and the caudal catheter was removed 1 hour later. During the delivery and the postpartum period, the estimated blood loss was about 700 ml and a total of 2000 ml of 5 percent dextrose in H_2O was infused. A total of 10 units of oxytocin (Pitocin®) was infused with the IV drip. The mother's postpartum course was benign and she was discharged in 6 days.

None of the guadruplets required more than suction and O_2 by face mask and bag for about 2 minutes. However, Baby C was grunting and had transient tachypnea and retractions. O_2 was administered and his

*Deseret Radiopaque Epidural, Deseret Pharmaceutical Company, Sandy, Utah.

TABLE 1
The First Set of Quadruplets (11/10/73)

	A	B	C	D
Method of delivery	Low forceps	Breech	Breech	Breech
Time of delivery	1641 hr	1646 hr	1653 hr	1700 hr
Sex	Female	Male	Male	Female
Weight, gm	2210	1800	1790	2010
Age at first breath, min	1	1	1	1
Age at first cry, min	1	3	2	2
Age at sustained respiration, min	1	1.5	1.5	1.5
Apgar 1 min	9	6	5	6
Apgar 5 min	9	9	9	9
Method of resuscitation	None	Bag and mask (1 min)	Bag and mask (1 min)	Bag and mask (45 sec)
Weight at discharge, gm	2185	2290	2220	2160
Date of discharge	11/28/73	12/3/73	12/3/73	11/26/73

initial blood gases on 40 percent O_2 showed a pH of 7.24, $Paco_2$ 44 torr, Pao_2 44 torr, and base excess −5. Four hours later, blood gases on room air showed pH 7.36, $Paco_2$ 40, Pao_2 48, and base excess −2. He progressed satisfactorily without need for intubation, and all quadruplets were discharged alive and well.

Case 2.—A 26-year-old Caucasian woman, 155 cm in height, gravida 2, para 1, conceived on human postmenopausal gonadotropins (Pergonal) and was closely followed as an outpatient. At 22 weeks gestation, a diagnosis of quadruplets was confirmed and she was admitted for close medical management and forestalling premature labor. Her hospitalization was uneventful except for two episodes of threatened premature labor at 28 weeks gestation and again 10 days later; both were controlled by IV alcohol administration. Because of her very distended abdomen and heavy burden, the patient was unable to care for herself during the last trimester.

On September 15, 1974, at 34 weeks gestation, the patient developed spontaneous labor. She weighed 68 kg and was markedly lordotic, with edema of back and lower limbs, BP 150/90, pulse rate 82, and a trace of proteinuria. At 2300, the cervix was 4 cm dilated and a caudal catheter was inserted in the left semiprone position. In 57 minutes, the cervix became fully dilated and she was ready for delivery. A test dose of 4 ml of 1.5 percent mepivacaine was injected through the caudal catheter, followed in 5 minutes by 15 ml of the same solution. She was then transferred to the delivery table, put in lithotomy position, uterus displaced to the left, and O_2 was administered. In 10 minutes, BP became 120/80 and analgesia level, using a pinprick, reached T_8 on the left and T_{10} on the right side.

Quadruplets were delivered in 42 minutes under adequate analgesia (table 2). Fifty-five minutes after the first dose of mepivacaine, the patient started to feel uncomfortable, and since obstetric difficulties were anticipated, the caudal block was "reactivated," using 15 ml of 0.5 percent bupivacaine.

Massive bleeding followed delivery of the fourth fetus. The uterus and cervix were intact but there were several vaginal lacerations. After 2 hours of attempting to control the bleeding with sutures, a vaginal pack was inserted and the patient was transferred to the Recovery Room. However, her condition deteriorated, a suprapubic mass was palpated and exploration under anesthesia was decided. Fifteen minutes before general anesthesia, she received 15 ml of 0.3 M sodium citrate in 20 percent syrup to raise the pH of the intragastric contents. In the operating room, 0.4 mg of atropine and 3 mg of d-tubocurarine were administered IV. Anesthesia was induced by "crash induction" using thiamylal (250 mg) followed by 100 mg of succinylcholine. Anesthesia was maintained with N_2O and O_2

TABLE 2
The Second Set of Quadruplets (9/16/74)

	A	B	C	D
Method of delivery	Low forceps	Breech	Mid-forceps	Mid-forceps
Time of delivery	2426 hr	2430 hr	2446 hr	0108 hr
Sex	Male	Female	Male	Male
Weight, gm	1550	1520	1440	1420
Age at first breath, min	1	1.5	1	1.5
Age at first cry, min	1	2	1	2.5
Age at sustained respiration, min	1	3	1	3
Apgar 1 min	8	4	8	4
Apgar 5 min	10	9	9	8
Method of resuscitation	None	Bag and mask (2 min)	None	Bag and mask (2 min)
Weight at discharge, gm	2100	2240	2140	2320
Date of discharge	10/17/74	10/17/74	10/23/74	10/23/74

(4:2), 2 ml of Innovar®, and succinylcholine drip. On removal of the vaginal pack, a hemocolpos was found. Evacuation of the hematoma revealed a spurting vaginal artery, ligation of which controlled the bleeding. The patient was then sent to the recovery room for observation. The total estimated blood loss, 2500 ml, was replaced by 7 units of blood. Urinary output was adequate. Thereafter, the patient's stay in the hospital was uneventful except for temporary mental depression. She was discharged on September 25, 1974, in good condition.

Babies B, C, and D developed mild respiratory distress syndrome at between 45, 50, and 60 minutes of age, respectively. Baby B required 24 to 30 percent O_2 with 5 percent $NaHCO_3$ for 1 day. Babies A and D developed transient hyperbilirubinemia that responded well to phototherapy. Baby D developed *E coli* sepsis, which was treated with antibiotics. All babies did well and left the hospital alive, each weighing above 2000 gm (table 2).

DISCUSSION

Many problems should be considered before choosing an anesthetic technic or drug for quadruplet delivery.

A. Maternal Problems.—Marked abdominal distention and a heavy uterus cause dyspnea and supine hypotensive syndrome; therefore, the parturient should stay on her side throughout labor, and the uterus should be displaced to the left throughout delivery. If epidural or caudal analgesia is used during labor, the patient is gently turned to the other side 10 minutes after injection of the local anesthetic, to obtain bilateral analgesia, where she stays until delivery time.

Marked lordosis due to abdominal distention makes flexion of the back and "opening" of the interlaminar spaces extremely difficult. Therefore, a midline approach for epidural or spinal is not advisable and a paramedian or lateral approach is required.

Superimposed toxemia, such as preeclampsia, is more common with multifetal gestation than in single pregnancy. Although the total blood volume in multiple gestation is higher than in single pregnancy, with toxemia complicating the former, the blood volume is less than expected.[21] Therefore, the mother with quadruplets may be hypertensive, hypovolemic, anemic, coagulopathic, edematous, and may excrete salt poorly. If toxemia occurs, certain precautions are required to avoid an excessively high block, hypovolemia should be corrected with plasma or low-salt plasma expanders rather than salt solutions, anemia should be corrected with packed red cells if required, blood coagulability should be closely followed, and blood components be readily available.

Bleeding may occur before, during, or after delivery because of premature separation of the placenta, increased obstetric interference, and/or postpartum uterine atony combined with a large placental site. Close observation of the mother, particularly in the postpartum period, is essential.

The patient is usually confined to bed during the latter part of her pregnancy. Thus, edema of the back, with or without toxemia, is not infrequent, adding to the difficulty of lumbar epidural or subarachnoid block. Therefore, the mother's back should always be examined early in labor before deciding on the anesthetic technic.

Mental depression is more common than with single pregnancy because the mother feels it will be difficult to raise four children at the same time. She is bored with the early hospitalization and suffers discomfort, dyspnea, and difficulty in moving. The obstetric team, including the anesthesiologist, should be cheerful and encouraging. Social workers and public relations personnel play an important role in supporting the mother mentally and providing means to support the family financially.

B. Fetal Problems.—Quadruplets have a high perinatal mortality and morbidity rate, and anesthesia should not be an added factor.

Because of uterine overdistention, premature labor is a major problem. Because of the limited blood supply, intrauterine growth retardation is common.[19] "Transfusion syndrome," or intrauterine "stealing," can cause problems to one fetus or more, leading to further growth retardation and anemia.[22] Contraction of the placental site or its premature separation following delivery of one or more fetuses can jeopardize the undelivered ones. These conditions make the fetuses highly susceptible to depressant drugs including anesthetics, limit their reserves, and make them easily susceptible to obstetric trauma.

Since depression secondary to general anesthesia is proportionate to the duration

and depth of anesthesia,[23] and since it takes longer to deliver four fetuses than one, general anesthesia is not the method of choice for vaginal delivery.

If the membranes are ruptured and the presenting part is not well engaged, prolapse of the umbilical cord can occur, requiring immediate interference. This problem is more frequent with multiple gestation because of the small size of the fetuses and high incidence of abnormal presentation. Adequate analgesia during parturition should therefore be available to allow for immediate intrauterine manipulation if cord prolapse occurs.

Obstetric manipulations are more common with multiple gestations than with single pregnancy, because of increased incidence of such conditions such as prolapsed cord, malpresentation, and interlocking. It is usually thought that drug-induced uterine relaxation is required for intrauterine manipulations; this is true for single pregnancy, but with multifetal gestation, uterine relaxants are not required because the uterus is usually very distended, the fetuses are usually small, and drugs such as halothane or ether add to the imminent danger of postpartum atony and hemorrhage.

To minimize obstetric manipulations, which increase maternal and fetal risks, the mother's ability to bear down should be preserved. Therefore, drugs that interfere with her state of consciousness or motor power should be avoided.

C. Anesthetic Problems.—Anesthetic agents or technic used should not reduce the already compromised uterine blood flow. Therefore hypotension, supine position without left lateral displacement, alpha--stimulants, positive-pressure ventilation,[24] and alkalosis[25] should be avoided. Adequate oxygenation of the mother, preferably allowing a high F_{IO_2}, should be considered in any anesthetic technic for the delivery of quadruplets.

Considering all these problems and requirements, epidural analgesia combined with O_2 administration, seems best for delivering quadruplets. Combined lumbar and caudal epidural (double-catheter technic) is the ideal approach where segmental lumbar epidural is used for 1st stage of labor, and both lumbar and caudal epidural for the 2nd stage. However, in our cases, the patients were relatively comfortable during the 1st stage and technical difficulty in performing lumbar epidural was anticipated secondary to marked lordosis and edema of the back.

Caudal analgesia alone in these conditions proved satisfactory and should always be considered for the delivery of quadruplets, but there are cases in which caudal analgesia is difficult or impossible, owing to anatomic variations or extreme obesity. Provided the problems and requirements of quadruplet delivery are well understood, technics other than caudal have been safely used, depending on the circumstances and the experience of the anesthesiologist and other members of the obstetric team.

General anesthesia for cesarean section using thiobarbiturate, succinylcholine, intubation, N_2O-O_2, and muscle relaxant is satisfactory.[14,16] Continuous fractional spinal analgesia was described in one case,[8] but sudden severe hypotension and respiratory insufficiency can be a problem owing to the heavy uterus and the overdistention of the abdomen. No cesarean section for quadruplets has been reported under epidural analgesia.

ACKNOWLEDGMENT

The author's gratitude extends to Mrs. Pat Sands, MPH, for revising the manuscript, and to the Misses Kathy Kutzavitch and Anna D. Francis for secretarial help.

REFERENCES

1. Moffit J: Quintuple birth. Med Surg Rep 44:334, 1881

2. Nijhoff GC: A case of quintuplets. J Obstet Gynaec Brit Comm 6:32-34, 1904

3. Dafoe AR: The Dionne quintuplets. JAMA 103:673-677, 1934

4. Constantine MCE: A case of quadruplets. Brit Med J 2:1206-1207, 1935

5. Harrison EH: The Eynesburgy quadruplets. Brit Med J 2:1207-1208, 1935

6. Dawson JB: A case of quadruplets. J Obstet Gynaec Brit Comm 43:252-266, 1936

7. Ford N, Caruso G: Two unreported cases of quintuplet births, Canadian and Italian. Canad Med Assoc J 39:333-335, 1938

8. Ullery JC: Delivery of quadruplets by cesarean section under conditions of spinal anesthesia. JAMA 128:183-185, 1945

9. Digby IP: A case of quintuplet pregnancy. J Obstet Gynaec Brit Comm 61:94-95, 1954

10. Gibbs CE, Boldt JW, Daly JW, et al: A quintuplet gestation. Obstet Gynec 16:464-468, 1960

11. Berbos JN, King BF, Janusz A: Quintuple pregnancy. JAMA 188:813-816, 1964

12. Liggins GC, Ibbertson HK: A successful quintuplet pregnancy following treatment with human pituitary gonadotrophin. Lancet 1:114-117, 1966

13. Keast AC, Cooper GZ: The Tukutese quintuplets. S Afr J Obstet Gynec 5:43-48, 1967

14. Aiken RA: An account of the Birmingham sextuplets. J Obstet Gynaec Brit Comm 76:684-691, 1969

15. Campbell S, Dewhurst CJ: Quintuplet pregnancy diagnosed and assessed by ultrasonic compound scanning. Lancet 1:101-103, 1970

16. Lachelin GCL, Brant HA, Swyer GIM, et al: Sextuplet pregnancy. Brit Med J 1:787-790, 1972

17. Jewelewicz R, James SL, Finster M, et al: Quintuplet gestation after ovulation induction with menopausal gonadotropins and pituitary lutinizing hormone. Obstet Gynec 40:1-5, 1972

18. Reaney BV, Kaye BM: Delivering the Chicago quints. Contemp Obstet Gynec 1:81-88, 1973

19. McFee JG, Lord EL, Jeffrey RL, et al: Multiple gestations of high fetal number. Obstet Gynec 44:99-106, 1974

20. Bonica JJ: Principles and Practice of Obstetric Anaesthesia and Analgesia. Philadelphia, FA Davis Company, 1967, vol 1, p 605

21. Rovinsky JJ, Jaffin H: Cardiovascular hemodynamics in pregnancy. III Cardiac rate, stroke volume, total peripheral resistance and central blood volume in multiple pregnancy. Synthesis of results. Amer J Obstet Gynec 95:787-794, 1966

22. Rausen AR, Seki M, Strauss L: Twin transfusion syndrome. A review of 19 cases studied at one institution. J Pediat 66:613-628, 1965

23. Bonica JJ: Obstetric Analgesia and Anesthesia. Berlin, Springer-Verlag, 1972

24. Levinson G, Shnider SM, de Lorimier AA, et al: Effects of maternal hyperventilation on uterine blood flow and fetal oxygenation and acid-base status. Anesthesiology 40:340-347, 1974

25. Ralson DH, Shnider SM, de Lorimier AA: Uterine blood flow and fetal acid-base changes after bicarbonate administration to the pregnant ewe. Anesthesiology 40:348-353, 1974

PNEUMOPERITONEUM Pneumoperitoneum is most commonly secondary to perforation of an abdominal viscus. The authors describe two patients requiring high inflation pressures and PEEP who developed tension pneumothorax followed by pneumoperitoneum. It was speculated that air dissected through the aortic and inferior vena cava openings in the diaphragm ultimately finding its way into the peritoneal cavity. The etiology of pneumoperitoneum is difficult to determine in patients on ventilators who may be paralyzed or narcotized. The presence of a relationship between the inspiratory phase of the ventilator and accumulation of intraperitoneal air may support the diagnosis of pneumothorax and prevent an unnecessary exploratory laparotomy. *(Egan M, Boutrous A: Pneumoperitoneum following tension pneumothorax. Report of two cases. Crit Care Med 3:170-172 1975)*

We Salute . . .

Evan Lloyd Frederickson, M.D.

WHILE a bow tie, a warm smile, and a quiet "Southern drawl" are not unique in themselves, they are unique in characterizing one of the true gentlemen of our specialty, Dr. Evan L. Frederickson.

Evan was born in Spring Green, Wisconsin, and received his BS degree from the College of Agriculture at the University of Wisconsin in 1947. From 1943 to 1946, he served as a technician anesthetist for a United States Field Hospital in the Pacific. This duty influenced his return to the University of Wisconsin, from which he received his MD in 1950. Following an internship year at Walter Reed Army Hospital in Washington, DC, Dr. Frederickson migrated to Iowa City, where he completed his anesthesiology training with Dr. Stuart Cullen and acquired a Masters Degree in Science in 1953.

Between 1954 and 1965, Dr. Frederickson served twice on the anesthesiology faculty of the University of Kansas, with an interim period in Pharmacology and Anesthesiology at the University of Washington in Seattle. From 1965 to the present he has been at Emory University, where he currently is Professor of Anesthesiology, Professor of Allied Health Professions, and Professor of Pharmacology.

Dr. Frederickson is a member of 16 medical and honor societies, including Alpha Omega Alpha. He has contributed widely to the activities of the American Society of Anesthesiologists, the International Anesthesia Research Society, the Advisory Committee on Respiratory and Anesthetic Drugs of the FDA, and the Anesthesia Training Committee of the National Institutes of Health. He is a Past President of both the Kansas Anesthesiologists Society and the Greater Atlanta Society of Anesthesiologists.

Over the years, Dr. Frederickson's research interests have spanned the spectrum from chloroform to local anesthetics, as well as the current technologic advances in diagnostic procedures and biomedical research.

His ubiquitous interests, stimulating personality, and concern for improved patient care are evident throughout the 40 intradisciplinary publications bearing his name.

Although a devoted clinician and teacher, Evan makes time for weekly rounds of golf and for joining his charming wife, Ruth, in gardening. Those who have visited the Fredericksons in suburban Atlanta have seen ample reflections of this mutual interest in the meticulously "manicured" lawn and carefully pruned flowering shrubs which embellish their lovely home.

Evan and Ruth are the proud parents of three children. Mary is the oldest and has now been married for 4 years to Clinton H. Joiner, who is in the MD-PhD program at Duke University; Mary is also working on her PhD in History at the University of North Carolina. Helen, the second child, recently received her Masters degree in molecular biology in Boulder, Colorado, and was married a week after receiving her degree. She has been admitted to Emory University Medical School. Ed, the youngest, is a rising senior in chemistry and is working in the honors program in the Chemistry Department at Emory. Ed, like his father and sister, plans a career in Medicine, and will be applying for medical school this coming year.

Dr. Evan Frederickson, physician, academician, loving husband, father and friend, we salute you!

DIAZEPAM ELIMINATION The influence of age or hepatocellular disease on the disposition and elimination of diazepam was studied in man. In normal individuals, following diazepam (0.1 mg/kg intravenously or 10 mg orally) the terminal plasma half-life was age-dependent increasing linearly from about 20 hours at 20 years to nearly 90 hours at 80 years. The prolonged half-life was attributed to an increase in the initial distribution volume of the drug as diazepam plasma clearance showed no age-dependence. Therefore, despite the prolonged half-life with increasing age the constancy of plasma clearance suggests diazepam will not accumulate with chronic administration. Patients with alcoholic cirrhosis showed decreased plasma clearance of diazepam with over a two-fold increase in the drug half-life. Therefore, chronic use in these patients might result in drug accumulation. *(Klotz U, Avant GR, Hoyumpa A et al: The effects of age and liver disease on the disposition and elimination of diazepam in adult man. J Clin Invest 55:347-359, 1975)*

A Regional Anesthetic Approach for Renal Transplantation

CLARA L. LINKE, MD*
ROBERT G. MERIN, MD†
Rochester, New York‡

After consideration of surgical demands and patient condition, regional anesthesia is preferred for renal transplantation at the University of Rochester Medical Center. Of 75 consecutive cases, 64 were successfully managed with single high-dose spinal anesthesia (10 to 20 mg tetracaine, mean 16.5 mg). The technic avoids untoward effects of neuromuscular blocking drugs, iatrogenic pulmonary infection from anesthetic equipment, and problems with potent general anesthetics. Patients are made comfortable by judicious low-dose sedation. Cardiovascular instability and blood loss are not troublesome. There have been no permanent neurologic sequelae or postspinal headaches. The authors believe this technic produces minimal biochemical and physiologic derangement for renal transplantation in the patient with chronic renal failure.

THE initial report on anesthesia for renal transplantation came from the Peter Bent Brigham Hospital in 1962.[1] Dr. Leroy Vandam reasoned that, given the lower abdominal extraperitoneal surgical approach, continuous spinal anesthesia seemed a logical choice. Systemic effects of the local anesthetic was not a problem. Hypotension, in these hypertensive patients, was minimal, and neuromuscular blocking drugs were unnecessary. Tracheal intubation could also be avoided, thus lessening the risk of respiratory infection, an important consideration, since the most common complication leading to a fatal outcome in the uremic patient is infection, enhanced by immunosuppression after the transplantation.[2] There were no postspinal headaches nor neurologic sequelae in the series.

Another anesthesia pioneer in the field of transplantation, Dr. Gordon Wyant, reported his early experience from Saskatchewan.[3] Seeking advice from other anesthesiologists at the beginning of his series of renal transplants, Wyant could find no unanimity: "Because of the many contradictory statements and good reasons given for each argument by each source, we decided to develop our own initial technique based on such physiologic and pharmacologic factors as were evident or might reasonably be suspected to exist in this type of patient."[3] He also concluded that a regional technic offered the best solution.

In 1969 (in abstract form only), the group from the Peter Bent Brigham Hospital reported that they had abandoned their original concept of regional anesthesia for renal transplantation.[4] The use of routine hemodialysis produced such improvement in the clinical condition of the patient that regional anesthesia was no longer needed. The majority of anesthesiologists apparently have agreed with this viewpoint. Reported

*Assistant Professor.

†Associate Professor.

‡Department of Anesthesiology, University of Rochester School of Medicine, Rochester, New York 14642.

This study was supported in part by Dr. Merin's Research Career Development Award #HL31752, NIAID #72-2539, and the New York State Kidney Institute.

Paper received: 6/2/75
Accepted for publication: 7/24/75

series have relied heavily on neuromuscular blocking drugs for relaxation during intravenous or inhalational techniques.[5-15]

Although hemodialysis has made a marked change in the pathophysiology of the transplant recipient, many of the early problems still are pertinent. One major concern is the lack of renal excretion of drugs. While the use of neuromuscular blocking drugs for renal transplantation is widespread, there have been appreciable problems associated with their use. Gallamine has generally been avoided in view of its predominately renal excretion.[15] Although the disposition of d-tubocurarine does not depend on renal excretion, there have been numerous reports of prolonged paralysis after transplantation.[6,9,11-13,17] Miller and coworkers[18] found that pancuronium produced a prolonged depression of twitch height in a group of anephric patients during renal transplantation, but that reversal with neostigmine was without difficulty. Concern with the use of succinylcholine has been the hyperkalemic effect of this drug. When marked hyperkalemia existed before the use of succinylcholine, significant rises were reported in serum K^+, particularly with the second dose.[19-21]

Several groups have referred to the bleeding disorders associated with chronic renal failure and dialysis. Rabiner, reviewing uremic bleeding, concluded, "It is now apparent that the major coagulation defect of uremic patients is a reversible platelet dysfunction. . . . With frequent hemo- or peritoneal dialyses the platelet abnormality can be corrected and normal hemostasis maintained."[22]

Peripheral polyneuropathy is clinically evident in many uremic patients, primarily as distal sensory and motor changes, most commonly peroneal and median nerve distributions. A generalized slowing of nerve conduction constitutes an integral part of the uremic syndrome, probably due to the inhibition of sodium transport.[23] Peripheral neurons undergo degeneration and secondary demyelination of axonal cylinders. Reversal of these changes has been documented after successful transplantation, though at varying time intervals.[23,24] Bromage observed a 38% shorter duration of local anesthesia in a report on brachial plexus block for AV fistula creation in uremic patients.[25] He attributed this to high compensatory cardiac output rather than to neuropathy. Apparently the neuropathy did not make the nerves more vulnerable to local anesthetics.

Although liver dysfunction is not an ubiquitous finding in patients with chronic renal failure on dialysis, there is an appreciable incidence of serum hepatitis.[2] The combination of hepatic and renal dysfunction may well be responsible for the problem with the disposition of various drugs in this group. Further consideration is the association of hepatic dysfunction with halogenated anesthetic agents. Although the relationship is far from clear, it seems judicious at this time to avoid repeated anesthetic procedures with these drugs.[26] Since many patients in chronic renal failure undergo repeated anesthesia, both elective and emergent,[15] the use of nonhalogenated drugs or other technics is advisable where possible.

Hemodialysis often results in effective relief of hypertension for many patients, so that the complications of hypertensive vascular disease are less frequently a problem than formerly. Unresponsive hypertension is currently one of the indications for prior bilateral nephrectomy.[15]

The biochemical disturbances produced by advanced renal failure can be fairly well controlled by effective dialysis. Nevertheless, the transplant recipient often presents with hyperkalemia and metabolic acidosis,[7] particularly if the donor kidney is from a cadaver and the timing of hemodialysis cannot be planned.

The anemia of chronic renal failure is not ameliorated by hemodialysis.[27] For an elective procedure, red blood cells can be given to the patient during the antecedent dialysis, but the recipient of a cadaver kidney is likely to present with severe anemia.

Improvement in perfusion and preservation technics for cadaver kidneys has prolonged the acceptable interval between harvest and transplantation. However, as the procedure is still considered urgent in many centers, many patients will come to operation with a full stomach. Most reporting groups have advocated "crash induction" technics.

Although the patient in chronic renal failure may be on a variety of drugs, successful hemodialysis often allows cessation of most potent medications. Some patients still need pharmacologic blood pressure control, however, so this aspect of their history must be

considered. Immunosuppressive therapy with corticosteroids, azathioprine, and/or immunoglobulin is routine at the time of transplantation.

The most commonly quoted reasons for avoiding regional anesthesia for renal transplantation have been: (1) neurologic sequelae from either abnormal bleeding at the time of the regional block or preexisting neuropathy; both have already been discussed,[22-25] (2) the psychologic state of the patient combined with the length of the procedure, and (3) instability of the cardiovascular system during regional anesthesia. These latter objections will be considered in our series of patients.

The advantages of the technic include: (1) an ideal surgical field without worry about untoward effects of neuromuscular blocking drugs, (2) avoidance of tracheal intubation, (3) relative safety in the patient with a full stomach, (4) no concern about interaction of acidosis and hyperkalemia with the anesthetic and adjuvant drugs, and (5) awake, reactive, comfortable patients in the immediate postoperative period.

Weighing all these considerations, we concluded that regional anesthesia was the most logical technic for renal transplantation. The following describes our experience with 75 consecutive renal transplantations from August 1968 to November 1974 (table).

TABLE
Renal Transplantation
University of Rochester Medical Center
75 Cases from August 1968 to December 1974

Male	43	Age: 10-14	7
Female	32	15-29	29
		30-39	21
		40-49	15
		50-57	3

Anesthesia technics: planned approach

	Spinal	Continuous epidural	General and continuous spinal	General
Number of cases (total 75)	64	5	1	5
Donors				
Live—20	16	1	0	3
Cadaver—55	48	4	1	2
Duration of surgical procedure				
2 to 4 hours	32	1	0	3
4 to 6 hours	32	4	1	2
Sedation				
IV only	33	1		
IV-N_2O insufflation	27			
Inhalation	4	4	1	5
Neuromuscular blocking drug	3	1	0	1
Endotracheal intubation	1	1	1	3

METHODS

Preanesthetic Considerations.—At the time of the initial visit with the patient (usually soon after acceptance into the transplant program), the whole procedure was discussed and a preliminary choice of anesthetic was made. In general, patients were stable on two or three weekly hemodialyses, with reasonable blood pressure control. Thirteen patients needed antihypertensive drug therapy (11 a-methyldopa, 2 propranolol). The only other maintenance drugs were digitalis (8) and prednisone (2): 2 patients were insulin dependent diabetics. Live related transplants were scheduled on the day following routine hemodialysis during which frozen red blood cells were transfused to bring the hematocrit to about 25%. For cadaver transplants, frozen red cells were also transfused pre-operatively if hematocrit values were below 25%.

Anesthetic Protocol

1. Regional Technique.—At the beginning of the series, the surgical procedure routinely lasted longer than 4 hours. In view of this, we initially employed continuous lumbar epidural anesthesia. However, 4 of the first 5 patients required general anesthesia supplementation. A single high dose spinal was used for the 6th patient. The case proceeded so smoothly that we preferred this technique thereafter.

Tetracaine in 5% dextrose was used in a single dose. We discovered that increasing the dose prolonged the duration of the block. Thus we used 18 to 20 mg of tetracaine in a tall patient and 14 to 16 mg in shorter patients, generally women and teenagers. Epinephrine (0.2 to 0.4 mg) was added. Spinal levels of T 6-4 were sought. The early orientation of each patient was of great aid in assuring him about the regional procedure. In addition, patient-to-patient advice was often helpful. Nevertheless, since none of the operations lasted less than 2 hours, some supplementation was always

necessary. The use of small intermittent IV doses of Innovar® (total dose 2 to 5 ml) and diazepam (total dose 5 to 10 mg) produced the desired sedation while maintaining voice contact. Close observation of respiration was particularly stressed. When supplemental O_2 was needed, it was given with a disposable inhalation therapy mask. If the surgical procedure lasted over 4 hours, some patients received 50% N_2O also through the same plastic mask.

2. General Anesthesia.—General anesthesia was selected for the 3 younger children in this series and 2 adults. The need for intraoperative and postoperative assisted ventilation in one obese patient and a combined nephrectomy, splenectomy, and transplant in the other indicated the need for tracheal intubation for the adults. Light general anesthesia and continuous spinal anesthesia were employed for management of the latter case.

3. Monitoring.—The arteriovenous fistula bruit was monitored continuously to assure patency and as a cardiovascular monitor and was carefully guarded. Blood pressure monitoring has been predominately by cuff or Doppler rather than by cannulation. An electrocardiograph, preferably with a write-out capability to assess T-wave changes, was used in all cases. Central venous catheter placement through a forearm vein was successful in 56/75 cases.

4. Blood and Fluids.—5% dextrose and water was administered at approximately 0.3 ml/kg/hr using a minidrip infusion set. Blood loss was replaced as closely as possible with washed frozen red cells and albumin. Combined blood pressure, central venous pressure, and blood loss estimates guided replacement.

RESULTS

Of the 64 spinal anesthesias, 33 were managed with IV sedation alone. This comprised primarily those whose operation was completed within 4 hours. Twenty-seven others received N_2O insufflation via the plastic open-system mask. All these patients were drowsy or lightly sleeping but could be easily aroused by voice. Four patients given spinal anesthesia also received a general anesthetic (3 thiopental-N_2O and 1 halothane). As mentioned, 4/5 lumbar epidurals had to be converted to general. Of the 75 patients, 6 were intubated, and small doses of neuromuscular blocking drugs were used in only 5.

At some time during spinal anesthesia, 33/64 patients were hypotensive (greater than 25% decrease of the preanesthetic blood pressure). However, only 12/64 were hypotensive at the time of revascularization of the transplant. Of these, 3 had a systolic pressure of less than 100 torr when clamps were released. Forty-three of the 64 (67%) showed a significant rise in blood pressure within 10 minutes of revascularization; this has prompted an ongoing study of plasma renin concentrations during transplantation. No cardiac arrhythmias were observed.

Blood pressure could usually be managed by blood and albumin administration. Thirty-one patients received sympathomimetic amines, sometimes prophylactically at the time of spinal anesthesia or to restore the bruit of the AV fistula. Heparin was not used intraoperatively. More than 60% (47/75) received 1 unit or less of packed red cells and only 10 patients received more than 2 units. The largest transfusion totaled 6 units in one patient. We feel that this is an impressive argument against the supposed cardiovascular instability during regional anesthesia for renal transplantation.

The only neurologic sequela we encountered was urinary retention in one patient for 1 month which cleared spontaneously without associated neurologic findings. Several patients had significant uremic peripheral neuropathy preoperatively; the most severe had a predialysis history of footdrop which cleared after dialysis and transplantation. There were no spinal headaches or nausea. One documented pulmonary infection in the postoperative period (5 days) occurred after the combined nephrectomy-splenectomy-transplant procedure.

All patients were taken postoperatively to the renal transplant intensive care unit, where their relatively smooth immediate postoperative course was greatly appreciated by the personnel.

Patient acceptance of the technic has been most gratifying. Although, preoperatively, many patients were less than enthusiastic about the prospect of spinal anesthesia, they often remarked that the experience had been a positive one and subsequently gave positive reinforcement to prospective transplant recipients.

Spinal anesthesia did not add significantly to the morbidity or mortality in this series. Objections generally raised to spinal

anesthesia for renal transplantation (neurologic complications and cardiovascular instability) were not a problem. We believe this technic produced minimal biochemical and physiologic derangement for renal transplantation in the patient with chronic renal failure.

ACKNOWLEDGMENT

The entire dialysis and transplant team made the success of this series possible. In particular, we would like to recognize Drs. Allyn May, Richard Freeman, Charles Linke, and William A. Greene.

REFERENCES

1. Vandam LD, Harrison JH, Murray JE, et al: Anesthetic aspects of renal homctransplantation in man. Anesthesiology 23:783-792, 1962

2. Chisholm GD: Complications of renal transplantation. Proc Royal Soc Med 66:914-918, 1973

3. Wyant GM: The anaesthetist looks at tissue transplantation: three years experience with kidney transplants. Can Anaesth Soc J 14:255-275, 1967

4. Bastron RD, Bailey G, Deutsch S, et al: Anesthesia for patients with chronic renal failure for renal homotransplantation. Anesthesiology 30: 335, 1969

5. Dhuner KG, Lundberg H, Peterhoff V: Anaesthesia in renal transplantaticn. Scand J Urol Nephrol 2:31-35, 1968

6. Homi J, Smith ER: Anesthetic management for renal transplantation: some controversial aspects. Progress in Anesthesia. London, Proceedings II World Congress, 1968, pp 679-684

7. Fujita T, Miyazaki M: Anesthetic management of allo-transplantation of kidney for the patient with chrcnic renal failure: clinical study on acid-base, electrolytes and other metabolites. Tohoku J Exp Med 110:195-206, 1973

8. Hansen DD, Fernandes A, Skovsted P, et al: Cyclopropane anaesthesia for renal transplantation. Report of 100 cases. Br J Anaesth 44:584-589, 1972

9. Logan DA, Howie HB, Crawford J: Anaesthesia and renal transplantation: an analysis of fifty-six cases. Br J Anaesth 46:69-74, 1974

10. Monks PS, Lumley J: Anesthetic aspects of renal transplantation. Ann R Coll Surg 50:344-366, 1972

11. Aldrete JA, Daniel W, O'Higgens JW, et al: Analysis of anesthetic-related morbidity in human recipients of renal hemografts. Anesth & Analg 50:321-329, 1971

12. Latarjet J, Bouletreau P, Fraysse G, et al: Problémes posés par l'anesthésie dans les transplantectomies rénales. Anesth, Anal, Réan 30: 685-696, 1973

13. Smith BH: Anaesthetic problems of renal transplantation. Proc Royal Soc Med 66:918-920, 1973

14. Duvaldestin P, Vourc'h G: Problémes posés par l'anesthésie dans les transplantations rénales. Anesth, Anal, Réan 31:333-359, 1974

15. Estafanous FG, Porter JK, El Tawil MY, et al: Anaesthetic management of anephric patients and patients in renal failure. Canad Anaesth Soc J 20:769-781, 1973

16. Feldman SA, Cohen EN, Golling RC: Excretion of gallamine in the dog. Anesthesiology 30: 593-598, 1969

17. Katz J, Kountz SL, Cohn R: Anesthetic considerations for renal transplant. Anesth & Analg 46:609-613, 1967

18. Miller RD, Stevens WC, Way WL: The effect of renal failure and hyperkalemia on the duration of pancuronium neuromuscular blockade in man. Anesth & Analg 52:661-666, 1973

19. Miller RD, Way WL, Hamilton WK: Succinylcholine-induced hyperkalemia in patients with renal failure? Anesthesiology 36:138-141, 1972

20. Koide M, Waud BE: Serum potassium concentrations after succinylcholine in patients with renal failure. Anesthesiology 36:142-145, 1972

21. Walton JD, Farman JV: Suxamethonium hyperkalemia in uremic neuropathy. Anaesthesia 28:666-668, 1973

22. Rabiner SF: Uremic bleeding. Progress in Hemostasis and Thrombosis. Edited by (Theodore H.) Spaet, M.D. New York, Grune and Stratton, 1972, vol 1, pp 233-250

23. Nielsen VK: Peripheral nerve function in chronic renal failure. Acta Med Scand 194:445-462, 1973

24. Bolton CF, Baltzan MA, Baltzan RB: Effects of renal transplantation on uremic neuropathy. N Engl J Med 284:1170-1175, 1971

25. Bromage PR: Improved brachial plexus blockade with bupivacaine hydrochloride and carbonated lidocaine. Anesthesiology 36:479-493, 1972

26. Dykes MHM: Anesthesia and the liver. International Anesthesiology Clinics. Boston, Little, Brown and Company, 1970, vol 8

27. Slawson KB: Anaesthesia for the patient in renal failure. Br J Anaesth 44:277-282, 1972

Rapid Anesthesia Induction in Combat Casualties with Full Stomachs

ROBERT SAMUEL CROMARTIE, III, MD*

A series of 50 combat-injured patients given crash intubation for rapid induction of anesthesia is presented. The technic consisted of injection of 3 mg of d-tubocurarine and 0.4 mg of atropine IV, preoxygenation by face mask for 3 minutes, and then injection of sodium thiopental or ketamine, followed immediately by 60 to 80 mg of succinylcholine IV. Intubation was performed with a cuffed tube after cessation of spontaneous respirations and relaxation of the jaw. In the entire series there was no vomiting or aspiration on induction. Thirty-six patients were induced with thiopental and 14 with ketamine. Three patients given thiopental and 2 given ketamine had a fall in blood pressure to below 100 torr systolic. The average BP change was in a positive direction with both agents.

INDUCTION of anesthesia in patients with full stomachs and with significant blood loss is fraught with the hazards of vomiting and aspiration as well as sudden hypotension. The present study of 50 Vietnam War casualties who required emergency surgical procedures demonstrates that the "crash" intubation technic can be reasonably safe in such patients.

METHOD

The majority of the patients were treated at the 18th Surgery Hospital in Quang Tri, Vietnam, but a few were seen in the 93rd Evacuation Hospital in Long Binh or the 91st Evacuation Hospital in Chu Lai. All were treated during the period January-October 1971. Most were operated upon within hours of receiving their wounds, through the rapid rescue evacuation achieved by the Dustoff helicopter crews.

Patients were generally taken directly to the operating room from the emergency room after rapid resuscitation with IV infusions of crystalloids and/or blood. Crossmatch facilities were not available at the 18th Surgery Hospital, so only type-specific blood was given.

Upon arrival in the operating room, the patient's vital signs were taken, he was given 3 mg of d-tubocurarine and 0.4 mg of atropine IV and was preoxygenated (100% O_2) by face mask. Three minutes after curare administration, 14 patients were given IV ketamine 2.2 mg/kg of estimated body weight and 36 received 2.2 to 3.3 mg of thiopental, followed immediately by 60 to 80 mg of succinylcholine IV. Intubation was with a cuffed tube after spontaneous respirations had ceased and the jaw was relaxed.

Positive-pressure ventilation was not generally administered until after intubation (table). At the time of intubation, the oropharynx was inspected carefully for evidence of regurgitation. Immediately after intubation, blood pressure and pulse rate were taken and the patient was then given whatever agent had been selected for use during the remainder of the procedure.

RESULTS

All 50 patients treated by this technic were successfully intubated, the oropharynx

*Senior Resident, Department of Surgery, Louisiana State University School of Medicine, New Orleans, Louisiana 70112.

Paper received: 6/12/75
Accepted for publication: 7/9/75

TABLE

Technic for Rapid Induction of Anesthesia and Crash Intubation

1. Give d-tubocurarine 3 mg and atropine 0.4 mg IV
2. Preoxygenation with face mask and 100% O_2 x 3 minutes
3. Give IV ketamine 2.2 mg/kg or IV thiopental 2.2-3.3 mg/kg
4. Follow immediately with succinylcholine 60-80 mg IV
5. Wait for spontaneous respirations to stop and jaw to relax
6. Intubate with cuffed tube

in every case being free of any gastric secretions or food particles at the time of intubation. The 36 patients induced with thiopental as the principal agent required an average of 3.4 units of blood. Comparison between postinduction and preinduction BP revealed an average increase of +1.8 torr. Seven had a BP of 100 systolic or less at the initiation of induction, of whom 5 had a rise in BP, 1 had no change, and 1 had a fall from 100/80 to 90/65. Two patients with a BP greaer than 100 systolic had a fall to less than 100: in 1, from 120/70 to 80/? and in the other, from 130/80 to 90/50.

The 14 patients induced with ketamine received an average of 10.6 units of blood. They showed an average BP rise of 9 torr. Of these, 9 had a BP of 100 systolic or less at the time of induction, 4 experiencing a rise, 3 showing no change, and 2 having a fall (1 from 85/? to 75/45 and the other from 50/? to unrecordable). This last patient had received extensive injuries to liver, kidney, colon, small bowel, chest, and extremities. He survived the operation with a BP of 70/40 at the conclusion of anesthesia after 84 units of blood, but died the next day from continued hemorrhage after receiving a total of 108 units of blood. No patients given ketamine with a BP greater than 100 had a fall to below 100 systolic.

There were no intraoperative deaths in this series.

DISCUSSION

This study supports the thesis that crash intubation is an excellent technic for the prevention of vomiting and aspiration upon induction of anesthesia. This method minimizes the vulnerable interval during which the patient has lost his pharyngeal reflexes but has not yet been intubated. During the vulnerable period, should the patient vomit, aspiration would be likely.

The incidence of aspiration during anesthesia in patients who are not intubated or who are intubated with uncuffed tubes is high. Culver and associates[1] studied 300 such patients by placing Evans-blue dye in their stomachs 15 to 30 minutes before induction and inspecting the mouth, pharynx, larynx, trachea, and main bronchi with laryngoscope and by bronchoscopy at the end of the surgical procedure. Frank vomiting was noted in 8% of the patients, while the dye showed regurgitation to have occurred in 26.3% and aspiration in 16.3%.

One way to minimize regurgitation is to keep low the intragastric pressure. This pressure is greatest with the patient in a Trendelenburg position and least in reverse Trendelenburg.[2] The foot-down or head-up position has been recommended and used with good results during crash induction,[3,4] but in our study it was not used because of the risk of hypotension, since most of the patients were actively hemorrhaging at the time of induction. The head-down position affords some protection against aspiration should the patient vomit, but the incidence of vomiting is much greater and therefore the overall risk of aspiration is greater.

In the study by Culver's group[1] with the patient supine, regurgitation was found in 15.5 and aspiration in 13%, whereas in Trendelenburg, regurgitation was present in 41.4 and aspiration in 15.3%.

Succinylcholine was chosen as the paralyzing agent because of its rapid onset of action. The depolarization occurring with this drug is associated with fasciculations which may be prevented by prior infusion of a small dose of d-tubocurarine.

LaCour[5] evaluated intragastric pressures in patients given crash inductions before injection of succinylcholine and during fasciculations. He noted a mean rise in pressure of 4.6 cm H_2O, with a range of 0 to 25 cm H_2O increase. This rise was prevented by the infusion of d-tubocurarine (4 to 6 mg), 3 minutes before giving the succinylcholine. Similar results were obtained by Miller and Way.[6]

A number of reports describe cardiac arrhythmias or hyperkalemia[7-12] following succinylcholine administration. This rise in K^+ has been shown to be minimized by prior administration of d-tubocurarine.[11,13,14]

All patients were preoxygenated to help avoid hypoxia during the induction period. Forced respirations were not used before intubation for fear of forcing air into the stomach and thus increasing the risk of vomiting.

As the two anesthetic agents, thiopental and ketamine, used in this study were not randomly selected, no attempt will be made to compare the two. With both agents, the average BP change was in a positive direction.

Ketamine has been shown[15,16] to cause a rise in BP and pulse rate in normovolemic patients. Chasapakis and colleagues[17] reported similar results in 13 patients in shock, requiring an average of 1300 ml of blood and showing an average BP rise of 30 torr, with pulse rate increases of from 0 to 20 bpm.

In our series, pulse changes were not marked: average change was +4.3 bpm (range −20 to +28), the highest pulse rate being 140 (increased from 130). The BP rise in our series also was not as marked, probably due to the degree of exsanguination of the patients. Of the 2/14 patients induced with ketamine who experienced BP falls to levels below 100 systolic, both had hypotension and tachycardia prior to induction and were experiencing significant blood loss at the time of induction. (One required 8 units and the other 84 units of blood during the procedure.) Of 9 patients with an initial systolic BP of 100 or less, BP rose in 4.

REFERENCES

1. Culver GA, Makel HP, Beecher HK: Frequency of aspiration of gastric contents by the lungs during anesthesia and surgery. Ann Surg 133: 289-292, 1951

2. O'Mullane EJ: Vomiting and regurgitation during anesthesia. Lancet 1:1209-1212, 1954

3. Snow RG, Nunn JF: Induction of anaesthesia in the footdown position for patients with a full stomach. Br J Anaesth 31:493-497, 1959

4. Hodges RJH, Bennett JR, Tunstall ME, et al: General anaesthesia for operative obstetrics. Br J Anaesth 31:152-163, 1959

5. LaCour D: Prevention of rise in intragastric pressure due to suxamethonium fasciculations by prior dose of d-tubocurarine. Acta Anaesthesiol Scand 14:5-15, 1970

6. Miller RD, Way WL: Inhibition of succinylcholine-induced increased intragastric pressure by nondepolarizing muscle relaxants and lidocaine. Anesthesiology 34:185-188, 1971

7. Dowdy EG, Fabian LW: Ventricular arrhythmias induced by succinylcholine in digitalized patients: a preliminary report. Anesth & Analg 42:501-513, 1963

8. Lowenstein E: Succinylcholine administration in the burned patient. Anesthesiology 27:494-496, 1966

9. Belin RP, Karleen CI: Cardiac arrest in the burned patient following succinyldicholine administration. Anesthesiology 27:516-518, 1963

10. Miller RD, Way WL, Hamilton WK, et al: Succinylcholine-induced hyperkalemia in patients with renal failure? Anesthesiology 36:138-141, 1972

11. Weintraub HD, Heisterkamp DV, Cooperman LH: Changes in plasma potassium concentration after depolarizing blockers in anaesthetized man. Br J Anaesth 41:1048-1052, 1969

12. Roth F, Wuthrich H: The clinical importance of hyperkalaemia following suxamethonium administration. Br J Anaesth 41:311-316, 1969

13. Mazze RI, Escue HM, Houston JB: Hyperkalemia and cardiovascular collapse following administration of succinylcholine to the traumatized patient. Anesthesiology 31:540-547, 1969

14. Aldrete JA, Zahler A, Aikawa JK: Prevention of succinylcholine-induced hyperkalaemia by magnesium sulfate. Can Anaesth Soc J 17:477-484, 1970

15. Lotfy AO, Amir-Jahed AK, Moarefi P: Anesthesia with ketamine: indications, advantages, and shortcomings. Anesth & Analg 49:969-974, 1970

16. Wilson RD, Traber DL, McCoy NR: Cardiopulmonary effects of Cl-581—the new dissociative anesthetic. South Med J 61:692-696, 1968

17. Chasapakis G, Kekis N, Sakkalis C, et al: Use of ketamine and pancuronium for anesthesia for patients in hemorrhagic shock. Anesth & Analg 52:282-287, 1973

Circulatory Changes During Anesthetic Induction: Impact of d-Tubocurarine Pretreatment, Thiamylal, Succinylcholine, Laryngoscopy, and Tracheal Lidocaine

ROBERT K. STOELTING, MD*
CHRISTINE PETERSON, RN†
Indianapolis, Indiana‡

Circulatory changes after IV d-tubocurarine (3 mg), thiamylal (4 mg/kg) plus succinylcholine (2 mg/kg) and followed by direct laryngoscopy with or without intratracheal lidocaine spray (2 mg/kg) just before endotracheal intubation (EI), were measured in 40 adult patients. Pretreatment with d-tubocurarine did not alter mean arterial pressure (MAP), heart rate (HR), or central venous pressure (CVP). One minute after thiamylal-succinylcholine and just before laryngoscopy, MAP was 15 torr less than the awake value ($p<0.05$) and HR was 13 beats/min greater than the awake value ($p<0.05$).

Laryngoscopy and EI elevated MAP above awake levels and further increased HR in all patients. The magnitude of these responses immediately following EI was not altered by tracheal lidocaine. However, the pressor and HR changes following EI were more transient when tracheal lidocaine was used (20 patients) and these patients were more likely to tolerate the tracheal tube without immediate additional anesthesia. The incidence of ventricular dysrhythmias was not altered by tracheal lidocaine. Compared with awake values, the cardiac index did not change significantly following intubation but stroke volume was decreased ($p<0.05$), with or without tracheal lidocaine.

RAPID production of anesthesia with an IV thiobarbiturate followed by succinylcholine and endotracheal intubation (EI) is a frequently used anesthetic induction technic. However, cardiovascular depression from the barbiturate[1] and/or a reflex sympathetic nervous system response to mechanical stimulation of the upper airway (increased BP, heart rate [HR], and dysrhythmias) during direct laryngoscopy[2-4] may occur. Nevertheless, in daily practice we rarely observed marked falls in BP after rapid thiamylal plus succinylcholine administration. Furthermore, the subsequent pressor and HR response to laryngoscopy and EI seemed transient, and ventricular dysrhythmias were infrequent. Therefore, we decided to quantitate circulatory changes occurring during a commonly used induction sequence with d-tubocurarine pretreatment, thiamylal plus succinylcholine followed by direct laryngoscopy, with or without intratracheal lidocaine spray just before EI.

METHODS

Forty normotensive adults (42 ± 6 yr, 67 ± 4 kg, mean ± SE) were studied in the supine position before elective operation. All were considered to be in ASA physical status I or II and free of organic heart disease. Each patient received intramuscular

*Associate Professor of Anesthesiology/Pharmacology.
†Anesthesia Research Nurse.
‡Indiana University School of Medicine, Indianapolis, Indiana 46202.

This study was approved by the Indiana University School of Medicine Clinical Research Committee.
Paper received: 1/27/75
Accepted for publication: 5/21/75

morphine (8 to 12 mg) and atropine (0.4 mg) about 60 minutes before arrival in the operating room. A radial artery and external or internal jugular vein were cannulated, and pressures were recorded continuously as was ECG lead 2. After breathing pure O_2 via an anesthesia face mask for 3 minutes, mean arterial pressure (MAP), central venous pressure (CVP), cardiac output (indocyanine green dye and Beckman cardiodensitometer), and HR were measured. Cardiac index (CI), stroke volume index (SVI), and systemic vascular resistance (SVR) were calculated.

d-Tubocurarine (3 mg IV) was then administered. Three minutes later, thiamylal (4 mg/kg) was given IV, followed by succinylcholine (2 mg/kg). All drugs were administered rapidly as a bolus through plastic tubing leading to a 5 cm Teflon catheter (16 or 18 gauge) in a forearm vein. Flush solution (lactated Ringer's 5 ml) was injected after each drug to insure rapid entrance into the circulation. Ventilation was manually controlled via the anesthesia face mask within 15 to 30 seconds after thiamylal-succinylcholine. One minute after thiamylal-succinylcholine administration, laryngoscopy (straight laryngoscope blade) and EI were performed.

During laryngoscopy, but before placement of the endotracheal tube, 2 mg/kg of 4 percent lidocaine (LaryngoTracheal Anesthesia Kit*) was sprayed into the tracheas of 20/40 patients (group I-A). No tracheal lidocaine was used in the other 20 patients (group I-B). Following EI, the endotracheal tube cuff was inflated with air until air leak around the tube during positive pressure was just eliminated. Ventilation was then controlled with a volume ventilator delivering pure O_2 until 5 minutes after thiamylal-succinylcholine. Controlled ventilation with O_2 was continued beyond 5 minutes in 10 patients from both groups I-A and I-B until either spontaneous movement occurred or 10 minutes elapsed after thiamylal-succinylcholine administration.

*Abbott Laboratories, North Chicago, Illinois.

Data were analyzed by Student's *t*-test, $p<0.05$ being considered significant.

RESULTS

Pretreatment with d-tubocurarine (3 mg) did not alter awake MAP, HR, or CVP (table 1). Maximum MAP decreases averaged 20 torr ($p<0.05$; range 0 to 52 torr) and occurred 43 ± 2 seconds (20 to 60 sec) after administering thiamylal-succinylcholine. This produced a MAP less than 60 torr in only 2 patients. In one of these patients, MAP decreased from 69 torr awake to 44 torr, and in the other, MAP decreased from 108 torr awake to 56 torr. One minute after thiamylal-succinylcholine administration, or immediately before starting laryngoscopy, MAP was 15 torr less ($p<0.05$) than the awake value and HR was increased 13 beats/min ($p<0.05$).

Laryngoscopy and EI reversed the decreased BP and further increased HR (table 2). The average duration of laryngoscopy to accomplish EI was similar in groups I-A and I-B. Maximum MAP increases above awake levels between 1 and 2 minutes after thiamylal-succinylcholine and in association with laryngoscopy and EI were 30 torr ($p<0.05$; 0 to 84 torr) 21 seconds after completion of laryngoscopy (group I-A, tracheal lidocaine) and 37 torr ($p<0.05$; 0 to 86 torr) 15 seconds after completion of laryngoscopy (group I-B, no tracheal lidocaine). MAP a few seconds later (corresponding to 2 min after thiamylal-succinylcholine) remained similarly elevated.

TABLE 1

Awake Pretreatment With d-Tubocurarine Followed by Thiamylal-Succinylcholine
Mean ± SE

	Before d-tubocurarine	3 minutes after d-tubocurarine	1 minute after thiamylal-succinylcholine	Age	Weight, kg	Thiamylal, mg	Succinylcholine, mg
Group I (n = 40)				42 ± 6	67 ± 4	268 ± 20	134 ± 10
MAP, torr	98 ± 22	97 ± 3	83 ± 3*				
HR, beats/min	75 ± 3	75 ± 3	88 ± 2*				
CVP, torr	6.9 ± 0.7	6.9 ± 0.8	8.4 ± 0.7				

*$p < 0.05$ compared with awake value.
n = number of patients.

TABLE 2

Minutes After Thiamylal-Succinylcholine (Laryngoscopy and Endotracheal Intubation Starting at 1 Minute)
Mean ± SE

	Awake*	1	2	3	5	Duration of direct laryngoscopy, sec
Group I-A (n = 20, tracheal lidocaine)						
MAP, torr	97 ± 3	79 ± 4†	124 ± 6†	122 ± 6†	102 ± 4	27 ± 5
HR, beats/min	75 ± 5	87 ± 4†	99 ± 4†	94 ± 3†	86 ± 4	
CVP, torr	6.1 ± 0.7	7.6 ± 1.1	9 ± 1.1	9.5 ± 1.4	9.3 ± 1.7	
CI, L/min/m^2	3.7 ± 0.4			3.9 ± 0.5		
SVI, ml/beat/m^2	49 ± 3			41 ± 3†		
SVR, torr/L/min/m^2	25 ± 2			29 ± 3		
Group I-B (n = 20, no tracheal lidocaine)						
MAP, torr	99 ± 4	88 ± 3†	133 ± 5†	128 ± 5†	124 ± 5†‡	28 ± 7
HR, beats/min	75 ± 4	88 ± 3†	103 ± 4†	103 ± 4†	100 ± 4†‡	
CVP, torr	7.8 ± 1.3	9.2 ± 1.1	9.7 ± 1.3	9.6 ± 1.3	9.9 ± 1.3	
CI, L/min/m^2	3.5 ± 0.4			3.8 ± 0.4		
SVI, ml/beat/m^2	47 ± 4			37 ± 3†		
SVR, torr/L/min/m^2	26 ± 3			31 ± 4		

*Since d-tubocurarine did not change MAP, HR, or CVP, only awake values before d-tubocurarine are shown.

†$p < 0.05$ compared with awake value.

‡$p < 0.05$. Group 1-B vs Group 1-A.

n = number of patients.

Maximum HR increases shortly after laryngoscopy and EI (for example, 2 min after thiamylal-succinylcholine) were 24 beats/min ($p<0.05$) and 28 beats/min ($p<0.05$) above awake values in groups I-A and I-B, respectively. The differences in HR and BP responses between the two groups were not statistically significant. Transient premature ventricular contractions (PVCs) occurred in 3 patients (group I-A, 2 patients; group I-B, 1 patient) during or within 1 to 2 minutes following laryngoscopy and EI. Three minutes after thiamylal-succinylcholine, SVI was significantly decreased in both groups but the elevated HR maintained the CI slightly above awake levels. CVP increased a like amount ($p<0.05$) in both groups and corresponded to the initiation of positive-pressure ventilation 15 to 30 seconds after thiamylal-succinylcholine.

Five minutes after thiamylal-succinylcholine, the MAP and HR had returned toward awake values in those receiving tracheal lidocaine (table 2). In contrast, 5 minutes after thiamylal-succinylcholine administration to patients not receiving tracheal lidocaine, the MAP and HR remained significantly greater than awake values and the corresponding measurements in those receiving tracheal lidocaine. Ten patients not receiving tracheal lidocaine during laryngoscopy were reacting to the endotracheal tube between 5 and 8 minutes after thiamylal-succinylcholine. In contrast, 4/10 patients given tracheal lidocaine during laryngoscopy reacted spontaneously to the endotracheal tube 9 to 10 minutes after thiamylal-succinylcholine. The remaining 6 patients did not move despite the turning of their heads 45 degrees to the left and right 10 minutes after thiamylal-succinylcholine. Ulnar nerve stimulation (Peripheral Nerve Stimulator, 50 Hz) revealed some residual neuromuscular blockade in those patients not moving after 10 minutes.

DISCUSSION

A small dose of d-tubocurarine before anesthetic induction did not alter MAP or HR. Subsequent rapid IV administration of thiamylal (4 mg/kg) and succinylcholine (2 mg/kg) was associated with significantly lowered MAP and increased HR. However, the magnitude of these changes was usually clinically insignificant. For example, 1 minute after thiamylal-succinylcholine, the MAP was decreased 15 percent from awake values (98 to 83 torr) and HR increased 18 percent (75 to 88 beats/min). MAP decreased below 60 torr in only 2/40 patients.

Laryngoscopy and EI reversed the BP decrease and further elevated HR above awake levels in every patient. The magnitude of these responses immediately after intubation was not altered by intratracheal lidocaine spray just before placement of the tube in the trachea. This lack of influence of tracheal lidocaine was predictable, since the tracheal mucosa would not yet have been anesthetized. Furthermore, Takeshima's group[5] considered direct laryngoscopy and not EI as responsible for such circulatory responses. Nevertheless, Denlinger and coworkers[6] demonstrated that tracheal lidocaine 5 minutes before a second laryngoscopy and EI attenuated the BP and HR responses.

Systemic absorption after tracheal lidocaine spray (2 mg/kg) has been found to result in plasma arterial lidocaine levels less than 2 mcg/ml[7] during the period of our study (for example, the first 9 min after tracheal lidocaine). This concentration is below the level associated with direct myocardial depression[8] or that effective in the treatment of ventricular irritability.[9] Therefore, direct myocardial depression in our patients receiving tracheal lidocaine seems unlikely. Likewise, an antiarrhythmic effect was not documented, as PVCs after intubation were rare and short-lasting, with or without tracheal lidocaine.

Other efforts to prevent the circulatory responses to laryngoscopy have not been entirely successful or practical. For example, deep anesthesia reduced cardiovascular changes during laryngoscopy in one study,[3] but in another report 30 minutes of prior halothane did not change BP responses from those seen in patients intubated after thiopental plus succinylcholine.[10] Topical anesthesia did not abolish circulatory responses to EI[4] and in some instances the topical procedure itself produced significant BP changes.[11]

Only DeVault and associates[12] prevented HR and BP responses by administering phentolamine before laryngoscopy. It would seem reasonable to conclude that the transient circulatory responses to direct laryngoscopy and EI are probably innocuous in normotensive patients. Overzealous use of deep anesthesia, topical anesthesia, or depressant drugs, in an attempt to prevent changes caused by laryngoscopy and EI,

may ultimately introduce more hazard than the response it was intended to attenuate.[13]

The HR increase following thiamylal-succinylcholine, but before laryngoscopy, may represent a baroreceptor response to decreased MAP or a specific effect (possible sympathetic postganglionic stimulation)[14] of succinylcholine. The increased HR associated with succinylcholine administration and direct laryngoscopy may attenuate decreased cardiac output normally resulting from thiobarbiturate-produced reductions in the SVI. Indeed, CI following intubation was maintained near awake levels in the presence of an increased HR and decreased SVI.

We conclude that the anesthesia induction sequence described in this report did not produce excessive BP decreases in normotensive and normovolemic adults. The subsequent pressor and increased HR response to laryngoscopy and EI were transient, and ventricular dysrhythmias were infrequent. The duration, but not the magnitude, of the BP and HR responses was even further shortened by tracheal lidocaine at the time of intubation. Tracheal lidocaine also prolonged the period most patients tolerated the endotracheal tube without moving when additional anesthesia was not provided immediately after intubation.

REFERENCES

1. Conway CM, Ellis DB: The haemodynamic effects of short-acting barbiturates. Br J Anaesth 41:534-542, 1969

2. Forbes AM, Dally FG: Acute hypertension during induction of anaesthesia and endotracheal intubation in normotensive man. Br J Anaesth 42: 618-624, 1970

3. King BD, Harris LC, Greifenstein FE, et al: Reflex circulatory responses to direct laryngoscopy and tracheal intubation performed during general anesthesia. Anesthesiology 12:556-566, 1951

4. Wycoff CC: Endotracheal intubation: effects on blood pressure and pulse rate. Anesthesiology 21:153-158, 1960

5. Takeshima K, Noda K, Higaki M: Cardiovascular response to rapid anesthesia induction and endotracheal intubation. Anesth & Analg 43:201-208, 1964

6. Denlinger JK, Ellison N, Ominsky AJ: Effects of intratracheal lidocaine on circulatory responses to tracheal intubation. Anesthesiology 41: 409-412, 1974

7. Viegas O, Stoelting RK: (In press) Anesthesiology

8. Grossman JI, Cooper JA, Frieden J: Cardiovascular effects of infusion of lidocaine on patients with heart disease. Amer J Cardiol 24:191-197, 1969

9. Gianelly R, von der Groeben JO, Spivack AP, et al: Effect of lidocaine on ventricular arrhythmias in patients with coronary artery disease. New Engl J Med 277:1215-1219, 1967

10. Gauthier J, Bosomworth P, Page D, et al: Effect of endotracheal intubation on ECG patterns during halothane anesthesia. Anesth & Analg 41: 466-470, 1962

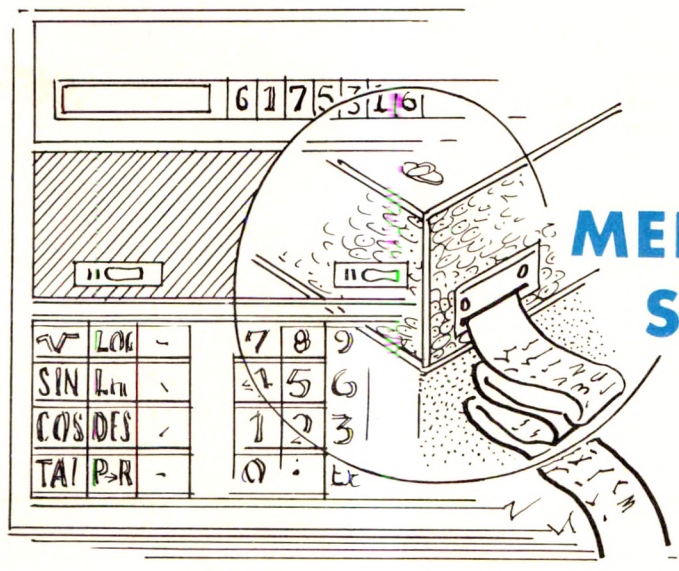
11. Ward RJ, Allen GD, Deveny LJ, et al: Halothane and the cardiovascular response to endotracheal intubation. Anesth & Analg 44:248-252, 1965

12. DeVault M, Greifenstein FE, Harris LC: Circulatory responses to endotracheal intubation in light general anesthesia—the effect of atropine and phentolamine. Anesthesiology 21:360-362, 1960

13. King BD, Elder JD, Proctor DF, et al: Reflex circulatory responses to tracheal intubation performed under topical anesthesia. Anesthesiology 15: 231-238, 1954

14. Galindo AH, Davis TB: Succinylcholine and cardiac excitability. Anesthesiology 23:32-40, 1962

PREVENTION OF CROSS-INFECTION BY GRAM-NEGATIVE BACTERIA (German). The increased use of mechanical appliances and aerosols has created favorable conditions for a rise in nosocomial infections, many of which could be avoided by proper aseptic technics. Tracheotomized patients are particularly at risk. Exhaustive study of recent world literature shows nebulizers to be the most frequently involved and to harbor the widest variety of organisms and pneumonia to lead the list of diseases contracted. The limits of efficacy in various disinfection and sterilization methods are described as a contributory factor in epidemics of cross-infections. *(Werner. Prakt Anäesth 9:316-330, 1974.)*



MEDICAL STATISTICS

Statistical Pearls. I. An Empty Shell Game

PATRICK D. HARRIS, PhD*

THE medical researcher, with a faithful student on his side, knelt at one end of a long hallway and carefully unrolled 30 meters of 8-channel polygraph paper on the floor. After a half-stooped but brisk walk alongside the "results" of the latest 4-hour experiment on blood flow in the pump-perfused dog, the perspiring investigator declared that there wasn't a single "typical response" in the whole record. The student suggested a calculation of a "mean response;" however, their array of old and dusty hardbacks on statistics did not treat the realities of intermittent sample times, unsynchronized measurements of several variables, shortened protocols, baseline drift, ruined blood samples, unanticipated hemorrhage sites, to name but a few.

Reluctantly, they made the much-dreaded trip to the classical statistician, which yielded the oft-heard, "You can't do that." "What kind of distribution do you have?" "We could try this if . . ." and "Why don't you repeat the study?" It is no wonder that a medical researcher, with his everyday, anything-but-standard data, feels like the carnival-goer who has just picked the empty shell for the tenth straight time.

At the gracious invitation of the Editors of *Anesthesia and Analgesia*, I have planned a series of articles to attempt to provide "statistical pearls" for many of the shells of data that realistic medical research gives to all of us. This series will treat several of the common statistical procedures with heavy doses of "intuitive feel" rather than rigorous derivations. I personally believe (or should I say that I am 95% confident) that much of the data from medical research does not meet the precise, theoretically-based requirements for a cookbook application of typical statistical procedures. (This

*Investigator, Dalton Research Center; Associate Professor of Physiology, University of Missouri School of Medicine, Columbia, Missouri 65201.

is especially true for the parametric tests which are the most commonly used procedures.)

How can the researcher decide whether or not it is appropriate to apply a specific statistical test for data which have already been collected? How much data (determinations, patients, animals, experimental groups, etc) are needed for a valid application of a certain statistical procedure? If the data do not quite fit a cookbook example, is there any statistical test that can be applied? Is there a special treatment for the one extreme data point in a large series of measurements? These, and many others, are questions which constantly arise for all, experienced and beginner, who are involved in the day-to-day collection of experimental data.

It is my intent to suggest practical approaches which will provide reasonable answers to these questions. What is reasonable? One approach is to be conservative. Suppose that I am not sure that my data meet the theoretic requirements for the application of a specific statistical test. In this case, I might use a less rigorous approach which is coupled with a "less than normal" chance (more stringent criterion) for accepting a statistically significant difference. This allows an individual to be comfortable that he has a real observation when he obtains a statistical difference even though his data do not fit a standard approach.

The foregoing description of "conservative" brings to mind the problem of defining statistical terms for the nonstatistician. This is a problem, because there are widely varying definitions even for such basic terms as statistics and statistical methods. Regardless of differences in precise definitions, there are two major divisions of statistics, descriptive and inferential.[1] Descriptive statistics are a mechanism for conveniently *describing* a large set of measurements, for *relating* one measurement to another, and for *exploring* general characteristics of the data. Typically, this form of statistics does not employ *t*-tests or levels of probability. In fact, one hardly even encounters the concept of a population versus a sample. Descriptive statistics do not provide a statistical answer to a scientific question; however, they can lead an individual to a question that can be answered.

Inferential statistics are a mechanism for *interpreting* several sets of measurements to reach a conclusion about a phenomenon, for *inferring* characteristics about unmeasured data, and for *directing* the course of additional measurements. This form of statistics requires the statement of a scientific question to be answered (a hypothesis to be refuted or accepted). To be more specific, inferential statistics involve the use of a limited number (sample) of people (or animals, excised organs, cell cultures, etc) to obtain a "good" estimate of the answer to a SPECIFIC QUESTION about the characteristics of a much larger number (population) of people, etc.

Success in the use of inferential statistics depends on the definition of the *population* and the *specific question* which then, and only then, defines an appropriate sample. In many situations, a "general" population will be defined by an experimental condition, eg, hemorrhagic hypotension, or a clinical procedure, eg, small-bowel resection, or a disease entity, eg, spongedivers disease (not exactly common in rural inland areas but nevertheless a very interesting population).

The "specific" population is defined by the specific question to be answered. Is there a difference between halothane and cyclopropane anesthesia with regard to the level of renal function during the first 6 hours following operation on the hemorrhagic hypotensive patient? For this specific question, the appropriate population does not include any past, current, or future patients who receive an anesthetic other than halothane or cyclopropane. The specific population does include all patients with hemorrhagic hypotension who undergo operation, regardless of the etiology of the hemorrhage or the type of surgical procedure. This specific population certainly includes all ages, both sexes, and remarkable as well as unremarkable medical histories.

The most important point is that a general population and a specific question enable the researcher to make a list of the characteristics, both general and detailed, which describe the specific population. Why make a list? This is the most effective way to answer, "Wait a minute, I'm really not interested in *that* population." This usually will lead to the choice of a more appropriate question for the population that really is of interest to the investigator.

Much of the time, inappropriate statistics surface in scientific publications in one of

three ways. First, purely descriptive statistics are used for major inferential purposes. Second, inappropriate inferential statistics are used because one has not stated a question to be answered. Third, raw data or minimally processed data are reported, when descriptive statistics would lead both the author and the reader to an important question which should be investigated by inferential statistics.

We all know that, many times, data are collected long before one thinks about the population, the question, or the characteristics of an adequate sample. Although this is not a desirable approach for inferential statistics, it does happen for many valid reasons. A patient "of interest" presents himself on short notice; one may not know how often a specific measurement can be made; an individual may not be sure that there will be anything of interest in the initial measurements. Data collected under these circumstances are a prime candidate for descriptive statistics in order to "discover" a question. Such a discovery leads to: "I thought that the shell of data was empty, but there really was a pearl of knowledge within."

REFERENCE

1. Dunn OJ: Basic Statistics: A Primer for the Biomedical Sciences. New York, John Wiley and Sons, Inc, 1964, pp 1-3

DEFIBRILLATION THRESHOLD The authors studied the influence of acid-base derangements on the external defibrillation threshold in dogs. Dogs were divided into 5 groups according to their acid-base state-respiratory acidosis, respiratory alkalosis, metabolic acidosis, hypoxia and control. Ventricular fibrillation was electrically produced and 90 seconds later the amount of energy necessary for electrical conversion was determined. Successful external defibrillation was possible in 75 per cent of all animals with 4 joules/kg or less. Thus, regardless of the acid-base status or arterial oxygenation prior to fibrillation, high energy levels were not necessary to achieve electrical conversion in most animals. However, the presence of metabolic acidosis and hypoxia impaired resumption of effective circulation following successful defibrillation. Hypercarbic animals had a high incidence of return suggesting that this derangement was not as detrimental to circulatory dynamics after electrical conversion. *(Yakaitis RW, Thomas JD, Mahaffey JE: Influence of pH and hypoxia on the success of defibrillation. Crit Care Med 3:139-142, 1975)*

Cardiovascular Effects of Enflurane and Halothane on the Rhesus Monkey

JOHN R. RITZMAN, Major, USA (MC)*
HOWARD H. ERICKSON, Lt Col, USAF (VC)†
EDWARD D. MILLER, JR, Major, USA (MC)‡
Fort Sam Houston, Texas

Ten rhesus monkeys were chronically instrumented to compare the cardiovascular effects of enflurane and halothane. In 17 experiments, each monkey was evaluated in the awake state and after equilibration at each of many anesthetic levels. End-expired gas concentrations were expressed in multiples of human minimum alveolar concentrations (MAC) for comparison.

There was a predictable dose-related decrease in heart rate, mean arterial pressure, peak left ventricular dp/dt, and the latter divided by left ventricular developed pressure $\left(\frac{dp/dt}{LVDP}\right)$ with both agents. Central venous pressure was increased by both. At equal MAC levels, no significant differences were detected between halothane and enflurane. Cardiac output and aortic flow acceleration were obtained on one of the animals for both agents. Results were consistent with those for the other measured parameters.

SINCE the appearance of enflurane as a new halogenated anesthetic agent, little agreement has been reached as to its effect on the cardiovascular system, and in particular, on the left ventricle. Both *in vitro* and *in vivo* studies (some unpublished) have produced conflicting results.[1-7] Some conflicts are explainable by differences in anesthetic concentration, experimental models, and choice of contractility index; others, however, involve very similar conditions employed by different groups of investigators.

In considering the use of enflurane for cardiac patients, it was concluded that more needed to be known about its effects on the healthy heart. The present study was designed to evaluate the effects of enflurane on the left ventricle in the intact nonhuman primate because of its similarity to man. Each primate was chronically instrumented to measure left ventricular pressure, aortic flow, and other parameters. Control recordings were obtained in the awake, unmedicated state; anesthesia was not complicated by the use of other drugs. Each

*Third Year Resident, Anesthesia and Operative Service, Brooke Army Medical Center, Fort Sam Houston, Texas; present address: Department of the Army, Headquarters, USA Medical Department Activity, Fort Leonard Wood, Missouri 65473.

†Environmental Sciences Division, USAF School of Aerospace Medicine, Brooke Air Force Base, Texas.

‡Staff Anesthesiologist, Anesthesia and Operative Service, Brooke Army Medical Center, Fort Sam Houston, Texas.

Read at the 49th Congress of the International Anesthesia Research Society, March 16-20, 1975, Hollywood, Florida.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of Army or the Department of Defense.

This study was supported in part by NASA Contract A-94544.

The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act of 1970 and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources—National Research Council.

Paper received: 6/20/75
Accepted for publication: 8/9/75

animal could be exposed to enflurane and to halothane, the latter being selected as the standard for comparison because of its wide use and well-known cardiovascular effects.

METHODS

Two weeks prior to experimentation, 10 healthy rhesus monkeys (3 to 4.2 kg) (Macaca mulatta) were instrumented through a left thoracotomy. They were premedicated subcutaneously with 0.04 mg/kg of atropine. Anesthesia was induced IV with thiopental sodium (35 mg/kg) and was maintained with a mixture of halothane-N_2O-O_2. Dosages of thiopental and atropine were consistent with current practice for experimental animal surgery.[8]

A Doppler ultrasonic flow probe was placed around the ascending aorta, a high-fidelity pressure transducer (Konigsberg Instruments, Pasadena, California) was implanted in the left ventricle, and ECG wires were sutured onto the epicardium. All leads were brought subcutaneously into a plastic photographic film container. In one end of the container, a 7-prong socket was mounted for the flow probe and ECG leads. Inside was sufficient room to house the pressure transducer plug and fluid-filled catheters when not in use. The container was cemented to a previously mounted skull pedestal similar to that described by Wolfe.[9]

Recovery required from 7 to 10 days, during which the animals received a regular monkey diet. One to 3 days prior to study, the monkeys were again anesthetized and heparin-filled central venous and carotid arterial catheters were inserted and exteriorized subcutaneously into the container.

On the morning of the experiment, the monkeys were restrained supine in a chair with which they had previously been familiarized. They were neither fasted nor medicated. After control recordings, anesthesia was induced by mask, using a Jackson-Rees apparatus. The trachea was intubated and the animal ventilated with an anesthetic-O_2 vapor at 15 ml/kg. The rate was adjusted to maintain the end-expired CO_2 between 4 and 5%, monitored with a Beckman LB-1 infrared analyzer.

The animals were maintained at an initial inspired concentration for 1 hour before recording, and at each subsequent concentration for 0.5 hour. At least 48 hours elapsed between exposures. Monkeys were alternated in the order in which they received the 2 agents, and also in the order of concentrations (light to deep versus deep to light in 0.25 MAC increments). In 5 experiments, the anesthetic sequence was repeated following beta-adrenergic blockade with IV propranolol (1 mg/kg). Our dosage of propranolol was based on the amount we have determined necessary to block a cardiac-rate response to isoproterenol (1 μg/kg). Up to 2 mg/kg of propranolol has been found to have little effect on the performance of the intact greyhound.[10]

Anesthetic levels were determined by gas-chromatographic analysis of end-expired samples and expressed in multiples of human MAC.[11,12] Standards were made after the method of Dobkin.[13] Data were recorded on analog magnetic tape and converted to digital form at 250 samples per second. The results of 10 consecutive cardiac cycles were averaged for each determination.

RESULTS

Data were compared in two different ways. First selected for analysis were those experiments for which recordings at control, near 1 MAC (light), and near 1.5 MAC (deep) were obtained. This involved 10 monkeys and included 6 exposures to halothane and 11 exposures to enflurane. Each variable for each agent was analyzed, using a 2-way analysis of variance, assuming no association between data collected on the same animal on different days.

All means and statistical results for these variables (table 1) show definite dose-related changes with either agent. For any of the variables measured, there was no significant difference between enflurane and halothane at control or at either MAC level. Comparisons between agents are unpaired.

Next, all available data were used to examine the linear relationship of each variable with MAC. The least-squares procedure was used to regress the dependent variable, "y," (for example, heart rate) on MAC values. The equation obtained was of the form $y = a + b\,(MAC)$, where a is the intercept and b is the slope. In the equations for heart rate (HR), maximum dp/dt, and mean arterial pressure (MAP) regressed on MAC (fig 1-3), the regression lines do not significantly differ between the two agents for any variable ($p < 0.05$). Equations and statistical information are shown in table 2.

For both agents, when a monkey received more than 1 exposure to an agent, data were

TABLE 1
Dose-Related Changes with Halothane and Enflurane

Variable	Halothane					Enflurane				
	Control (C)	Light (L)	Deep (D)	$\hat{\sigma}$ †	Probability levels for comparison	Control (C)	Light (L)	Deep (D)	$\hat{\sigma}$ †	Probability levels for comparison
MAC	0	0.93 (0.71-1.17)	1.56 (1.36-1.75)			0	1.00 (0.89-1.1)	1.52 (1.34-1.79)		
CVP,* torr	1.84* ±(.78)‡	3.13* ±(1.40)	4.19* ±(1.56)	0.719	C vs L NS C vs D $p < 0.05$ L vs D NS	1.59§ ±(0.36)‡	3.40§ ±(1.14)	3.86§ ±(1.24)	0.715	C vs L $p < 0.05$ C vs D $p < 0.01$ L vs D NS
MAP,* torr	98.47* ±(6.30)	55.90* ±(5.76)	26.07* ±(6.57)	7.644	C vs L $p < 0.001$ C vs D $p < 0.001$ L vs D $p < 0.01$	111.14§ ±(3.40)	56.38§ ±(5.64)	37.03§ ±(2.11)	5.352	C vs L $p < 0.001$ C vs D $p < 0.001$ L vs D $p < 0.01$
HR, bpm	195.0 ±(10.7)	152.5 ±(10.7)	117.0 ±(10.2)	6.52	C vs L $p < 0.001$ C vs D $p < 0.001$ L vs D $p < 0.001$	186.7 ±(6.4)	141.5 ±(6.4)	120.4 ±(2.8)	7.80	C vs L $p < 0.001$ C vs D $p < 0.001$ L vs D $p < 0.05$
Max dp/dt, torr/sec	4818.9 ±(349.4)	1487.0 ±(221.0)	626.2 ±(165.4)	297.568	C vs L $p < 0.001$ C vs D $p < 0.001$ L vs D $p < 0.05$	5228.0 ± (347.6)	1951.7 ±(336.0)	975.7 ±(142.8)	298.188	C vs L $p < 0.001$ C vs D $p < 0.001$ L vs D $p < 0.01$
dp/dt LVDP sec^{-1}	91.4 ±(4.1)	58.3 ±(5.2)	47.6 ±(7.2)	8.325	C vs L $p < 0.01$ C vs D $p < 0.001$ L vs D NS	91.2 ±(6.7)	64.2 ±(6.9)	52.4 ±(4.7)	7.302	C vs L $p < 0.01$ C vs D $p < 0.001$ L vs D NS

*N = 5; otherwise N = 6.

†Standard error, from two-way analysis, for testing between two means at different MAC levels with 2 (N-1) degrees of freedom.

‡Standard error of the mean.

§N = 9; otherwise N = 11.

†Standard error, from two-way analysis, for testing between two MAC level means with 2 (N-1) degrees of freedom.

‡Standard error of the mean.

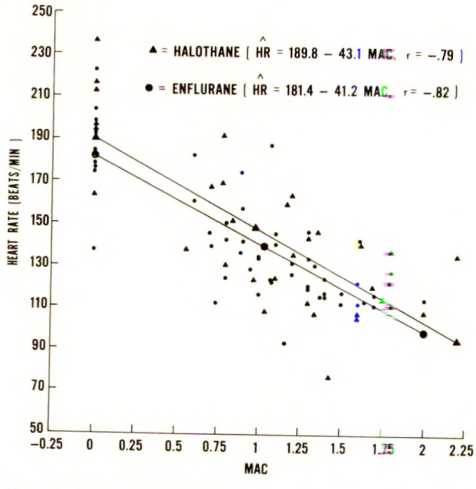


FIG 1. Heart rate (HR) regressed on MAC for halothane and enflurane separately.

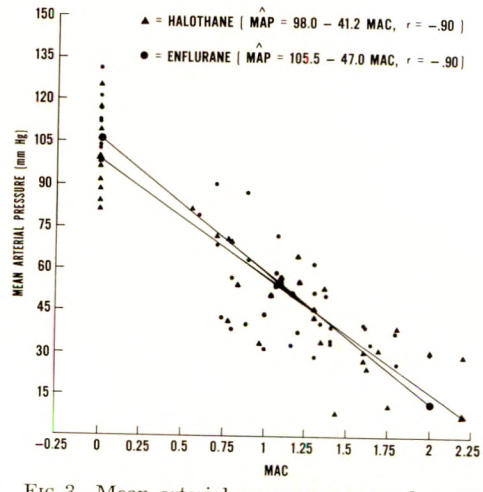


FIG 3. Mean arterial pressure regressed on MAC for halothane and enflurane separately.

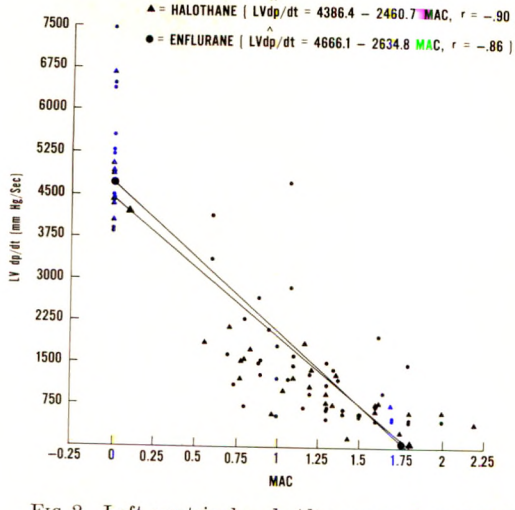


FIG 2. Left ventricular dp/dt regressed on MAC for halothane and enflurance separately.

treated as though from a different animal. This appeared to be justified from an inspection of the results.

Data were obtained from aortic flow measurements for only 1 animal at different MAC levels. Such flow-probe failures as occurred were in most instances the result of leakage of body fluids into the probes, leading to shorted circuits, and were caused by technologic maladroitness. These data and derived variables presented in table 3 substantiate the other findings reported in table 1.

DISCUSSION

Myocardial effects of enflurane have been studied in a variety of ways. Two groups of investigators used isolated cat papillary-muscle preparations. Brown and Crout[1]

TABLE 2

Regression Equations (see fig 1-3)

Anesthetic agent	Equation	Number of data pairs used	Standard error*	r†
Halothane	MAP = 97.99 - 41.22 MAC	35	13.80	—0.90
Enflurane	MAP = 105.50 - 46.96 MAC	45	13.48	—0.90
Combined	MAP = 101.91 - 44.09 MAC	80	13.62	—0.90
Halothane	HR = 189.8 - 43.09 MAC	35	23.30	—0.79
Enflurane	HR = 181.4 - 41.15 MAC	59	17.39	—0.82
Combined	HR = 184.7 - 42.11 MAC	94	19.82	—0.80
Halothane	LV dp/dt = 4386.4 - 2460.7 MAC	35	852.4	—0.90
Enflurane	LV dp/dt = 4666.1 - 2634.8 MAC	59	958.2	—0.86
Combined	LV dp/dt = 4548.2 - 2556.6 MAC	94	914.2	—0.87

*Based on deviations from regression line with N-2 degrees of freedom.

†Correlation coefficient—an index reflecting the degree of linear association betwen the two variables.

TABLE 3
Data from One Monkey at Different MAC Levels

Agent	MAC	HR, bpm	MAP, torr	CVP, mean, torr	Max dp/dt, torr/sec	Cardiac output, ml/min	Maximum aortic acceleration, cm/sec^2	Resistance MAP/CO, torr/ml/min^{-1}
Halothane	0	163	125	0.9	4287	591	2360	0.2115
	0.8	130	69	2.0	1542	452	1860	0.1527
	1.1	124	57	2.3	1212	459	1920	0.1242
	1.3	112	42	2.3	927	452	1340	0.0929
	1.6	107	27	2.2	739	390	1260	0.0692
	2.0	108	30	2.5	601	383	940	0.0783
Enflurane	0	192	130	0.5	5035	703	3400	0.1849
	0.9	141	63	1.6	1263	536	1720	0.1175
	1.2	131	50	1.9	918	522	1600	0.0958
	1.4	117	39	2.2	643	515	1300	0.0757
	1.5	115	35	2.4	576	466	1060	0.0730
	1.8	127	26	3.2	435	397	700	0.0655

found enflurane to be the most depressant of 5 general anesthetic agents. Shimosato's group[2] reported enflurane to be less depressant than halothane or methoxyflurane. When Shimosato's results are expressed in MAC as suggested by Saidman,[3] enflurane still remains less depressant than halothane.

In dogs, Shimosato[4] reported a shift to the left of the force velocity curve and a decrease in max dp/dt with enflurane, thus indicating negative inotropy. Tarnow[5] reported significantly decreased MAP, cardiac output, stroke volume, and max dp/dt with both halothane and enflurane, and concluded that the latter offers no cardiovascular advantage over halothane.

Etsten* reported that enflurane did not affect human right ventricular V_{max} or cardiac output. Dobkin[6] and Graves and Downs* found decreased cardiac output in humans under enflurane. Conversely, Rouge* reported increases in cardiac output with increasing depth of enflurane, attributing this to catecholamine release in response to a markedly elevated $Paco_2$.

Many indices[14,15] have been proposed to assess myocardial function, including max dp/dt, dp/dt/IP, and maximum aortic flow acceleration. Of these, nearly all are affected significantly by changes in preload, afterload, HR, and systemic resistance (SR). Reportedly unaffected is maximum intrinsic velocity (V_{max}).[16] This can be obtained from a left ventricular (LV) pressure tracing and its first derivative, dp/dt. However, we were unable to obtain consistently reliable V_{max} computations from these data, due at least in part to rapid heart rate.

Therefore, max dp/dt, dp/dt/LVDP and, where available, aortic flow data are reported. The awake monkey was its own control. Each was exposed to different anesthetics on different days under identical conditions. Changes in MAP, CVP, HR, and SR were the same for enflurane and halothane. This suggests that the major variables which may influence contractile measurements were similarly affected by both drugs. Therefore, the reported parameters should be valid indicators to compare effects of anesthetics on myocardial contractility. Although the data in table 3 suggest that cardiac output decreases with enflurane, additional experiments are needed to confirm these findings.

We gained the clinical impression that these nonhuman primates behave much the same as humans under these two clinically somewhat different anesthetics. The only notable exception is HR, which was decreased during anesthesia in these excitable small animals. Most investigators report an increasing HR with increasing depth of enflurane in humans. In the majority of

*Unpublished data to Ohio Medical Products.

human studies, however, the patient received a narcotic or barbiturate and an anticholinergic premedication. It is therefore difficult to say if a monkey's HR responds differently to enflurane than that of a human.

In 2 instances for halothane and 3 for enflurane, the anesthetic sequence was repeated following beta blockade with propranolol. Propranolol decreased max dp/dt by approximately 50% in the awake, conscious monkey. But while anesthetized by either agent, no appreciable change in dp/dt was brought about by the addition of propranolol. While there is insufficient data to justify a conclusion, one might speculate that both agents affect dp/dt by interfering with the sympathetic nervous system and specifically the beta-adrenergic response.

ACKNOWLEDGMENT

The authors thank Stephan H. Cramlet for surgical assistance, Laurence H. Pfeiffer for electronic assistance, E. L. Fitzpatrick for computer assistance, and Alton J. Rahe for statistical assistance.

REFERENCES

1. Brown BR, Crout RJ: A comparative study of the effects of five general anesthetics on myocardial contractility I. Anesthesiology 34:236-245, 1971

2. Shimosato S, Sugai N, Iwatsuki N, et al: The effects of Ethrane on cardiac muscle mechanics. Anesthesiology 30:513-518, 1969

3. Saidman LJ: The effect of Ethrane. Anesthesiology 31:386, 1969

4. Shimasato S, Dhen P-Y, Gilbert JB, et al: Effect of Ethrane on the performance of the left ventricle (abstract). Anesthesiology 30:351, 1969

5. Tarnow J, Gethmann JW, Hess W, et al: The influence of Ethrane on the hemodynamics and the oxygen supply of the myocardium in comparison to halothane. Anaesthesist 23:281-290, 1974

6. Dobkin AB, Heinrich RG, Israel JS, et al: Clinical and laboratory evaluation of a new inhalational agent: compound 347 (CHF_2-O-CF_2-CHFCl). Anesthesiology 29:275-287, 1968

7. Marshall BE, Cohen PJ, Klingenmaier CH, et al: Some pulmonary and cardiovascular effects of enflurane (Ethrane) with varying $Paco_2$ in man. Br J Anaesth 43:996-1002, 1971

8. Martin DP: Methods of anesthesia in nonhuman primates. Lab Anim Sci 22:837-843, 1972

9. Wolf JW: Technique for chronic head restraint and electrophysiologic recording in the awake rhesus monkey. Physiol Behav 13:461-464, 1974

10. Donald DE, Ferguson DA, Milburn SE: Effect of beta-adrenergic receptor blockade on racing performance of greyhounds with normal and with denervated hearts. Circ Res 22:127-134, 1968

11. Gion H, Saidman LJ: The minimum alveolar concentration of enflurane in man. Anesthesiology 35:361-364, 1971

12. Saidman LJ, Eger EI II, Munson ES, et al: Minimum alveolar concentrations of methoxyflurane with theories of anesthesia. Anesthesiology 28:994-1002, 1967

13. Dobkin AB, Kim D, Levy AA, et al: Studies on the calibration of enflurane vaporizers. Anesth & Analg 52:317-321, 1973

14. Mason DT: Usefulness and limitations of the rate of rise of intraventricular pressure (dp/dt) in the evaluation of myocardial contractility in man. Am J Cardiol 23:516-527, 1969

15. Noble MIM, Trenchard D, Guz A: Measurement and significance of the maximum acceleration of blood from the left ventricle. Circ Res 19:139-147, 1966

16. Shimosato S: Isovolemic intraventricular pressure change: an index of myocardial contractility during anesthesia. Anesthesiology 31:327-333, 1969

Guest Discussion

EVAN L. FREDERICKSON, MD
Anesthesia Research
Emory University
Atlanta, Georgia

Many writers have tried to describe the different effects of various interactions of anesthetic agents and the cardiovascular system. Each has presented data from a slightly different preparation, and conditions or concentrations have varied. As a result, arguments continue to flourish, with various individuals coming to different opinions via the work of the individual that happens to fit his own prejudices.

The very sophisticated study by Dr. Ritzman, using a primate preparation, concludes that there is little difference between the action of these two agents on the cardiovascular system. Dr. Ritzman, I believe, should be congratulated on coming to this conclusion, as it is probably closer to the truth than many of the differences that have been poorly defined in other studies.

However, there are some problems with his preparation that were not too well described. In spite of the fact that this is a primate, it obviously was a very frightened postoperative primate in the control period, with a heart rate of 185 to 200 at this particular time. Also, blood pressure was probably increased beyond normal with the mean pressure approximately 100 and over in each of the groups. The animals were obviously in a postoperative state with at least an inflammatory response around each

of the chronically implanted instruments and had catheters in at least two of their major vessels.

Since the advent of the halogenated anesthetic agents, there has been a great tendency among anesthesiologists to anesthetize the cardiovascular system, almost to the exclusion of other organ systems. This is evidenced by the fact that I notice residents frequently paying much more attention to the cardiovascular parameters than to the rest of the patient. This probably is not nearly so bad as we formerly thought, because we have found by experience that the depression of the cardiovascular system does seem to parallel the depression of the central nervous system or the production of what we call "anesthesia."

The difficulty of measuring "myocardial contractility," which is not defined in quantitative terms has led to a mass of correlative data. To use this type of evidence to make quantitative comparisons is probably not justified. However, "trends" or "patterns" developed by animal models or clinical situations may well be more easily predicted by the use of these measurements. The increasing use of computers that can process repetitive data with increasing speed can soon inundate the anesthesiologist with numbers and correlations. Thus these instruments should be used to give us matrix comparisons, tracking approaches and trend analyses. These technics may then be used to predict occurrences that the vigilant physician still may not diagnose until too late for optimum therapy.

Another very interesting portion of this paper is the report of the animals that received propranolol. Although the other cardiovascular parameters were not defined, it is stated that the change in dp/dt at least was not affected by the addition of anesthetic agents in an animal which could not respond with a change in sympathetic nervous system activity. This would also imply that the control state of the sympathetic nervous system activity may well influence the effect of the anesthetic agent on the myocardium.

Skovsted and Price[1] have demonstrated that enflurane, as well as halothane, fits into the group-2 type of anesthetic agents that cause a depression of the pressor center in the medulla with little effect on depressor reflexes. This is in contrast to ether, cyclopropane, and fluroxene, which produce a depression of the depressor reflexes with little depression of the pressor center—one of the surprising effects of enflurane, which also is an ether.

In conclusion, again I would like to congratulate Dr. Ritzman on his very sophisticated study that came up with an answer that I believe is clinically significant. Perhaps with further measurement at a clinical level, we will be able to find significant differences between the cardiovascular effects of these agents, but at present, we would have to come to the conclusion that both appear to depress myocardial contractility to a similar degree.

REFERENCE

1. Skovsted P, Price H: The effects of Ethrane on arterial pressure, preganglionic sympathetic activity and barostatic reflexes. Anesthesiology 36: 257-262, 1972

PHENCYCLIDINE Two cases of phencyclidine poisoning are described. Symptoms ranged from coma with hypotension to agitation and hallucinations. Treatment is supportive and a reduction of sensory stimulation. Naloxone or physostigmine were ineffective. Diazepam 0.1 mg/kg may be helpful in the severely agitated patient. Phencyclidine abuse should be considered in patients with unexplained acute psychosis, dystonic reactions, convulsions or coma. *(Tong TG, Benowitz NL, Becker CE et al: Phencyclidine poisoning. JAMA 234:512-513, 1975)*

Low-Dose Intramuscular Ketamine for Pediatric Radiotherapy: A Case Report

H. LAWRENCE AMBERG, MD*
GLENN GORDON, MD†
Los Angeles, California‡

Ketamine in low IM doses was found to produce satisfactory anesthesia for radiotherapy in a pediatric patient in a series of extended treatments. Change in anesthesiologists may have been a factor in increasing apprehension and anesthetic dosage in later treatments.

THE anesthesiologist is occasionally involved in the anesthetic management of the pediatric patient for radiotherapy. Assuring exact field irradiation often entails the use of head molds or face masks and requires that the patient be unattended during the radiation treatment period.

Multiple methods of anesthetic management have been advocated. Harrison and Bennet[1] used insufflation of N_2O-O_2-halothane mixture with fair results. Browne and associates[2] tried to refine this technic by using an elaborate frame to support the airway, while the child inhaled N_2O-O_2-halothane via an oral airway. Both these methods avoided repeated intubations, but required frequent multiple halothane exposures. The widely used Toronto mixture, or "lytic cocktail" (2.75 mg/kg of meperidine, 0.7 mg/kg of promethazine, 0.7 mg/kg of chlorpromazine), has the disadvantages of prolonged induction and recovery times and relative anorexia during this period.

The advent of ketamine has offered an additional method of patient sedation with three major advantages: Frequent halothane exposures are avoided, the prolonged induction and recovery time associated with the lytic cocktails is reduced, and an adequate airway is assured while the patient is left unattended. Bree and colleagues[3] demonstrated the safety of repeated ketamine administrations in the monkey, and Corssen and Oget[4] proved the feasibility of using ketamine for repeated dressing changes in the burn patient, while Sadove's group[5] showed the excellent analgesic properties of ketamine given in low IM doses. Not until 1972, when Cronin and coworkers[6] reported the use of ketamine in radiotherapy, did ketamine supplant inhalation agents and lytic cocktails as a safe and easy method of immobilizing pediatric patients for brief painless treatments.

Ketamine dosages previously recommended for anesthesia in radiotherapy have ranged from 2.6 to 22.3 mg/kg IM, with and without premedication, averaging in the 6 to 15 mg/kg range.[6-8] We have found that small doses are feasible, with a concomitant decrease in associated recovery time and morbidity.

CASE REPORT

A 16.4-kg boy with a retinoblastoma at age 37 months was treated promptly by surgical enucleation of the left eye. Five months later, recurrence of the tumor in the left socket was noted. A thorough medical evaluation, including brain and liver scans and a bone series, failed to elicit evidence of

*Resident.
†Professor.
‡Department of Anesthesia, Los Angeles County-USC Medical Center, Los Angeles, California 90033.
Paper received: 5/2/75
Accepted for publication: 7/9/75

metastases. Following a second excisional operation, the decision was made to irradiate the socket with 5600 rads.

Prior to the involvement of the anesthesia department, chlorohydrate and lytic cocktails were given without success: 1200 mg of chlorohydrate produced an ataxic state without sufficient anesthesia for treatment; a double dose of lytic cocktail (40 mg of meperidine, 40 mg of promethazine, 20 mg of chlorpromazine) produced similar effects, with the added disadvantages of markedly prolonged induction and recovery times.

The treatments required that the child be placed in a molded headrest with a loose-mesh fiberglass face mask (fig 1 and 2). During a 7-week treatment period (4/week), the patient received a total of 29 ketamine administrations: 28 sessions of 200 rads each, plus one preliminary session to determine field size and location. No premedication was administered prior to the first 13 sessions; however, to reduce the possibility of laryngospasm secondary to secretions, 0.3 mg of atropine was given orally 1 hour pretreatment for the remaining 16 sessions.

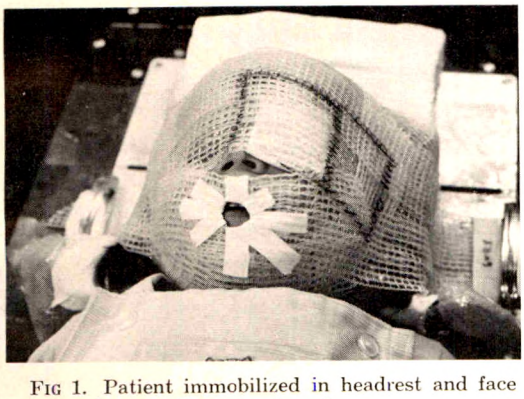


FIG 1. Patient immobilized in headrest and face mask and ready for a treatment.

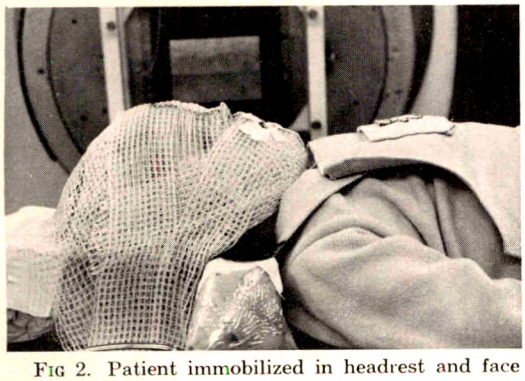


FIG 2. Patient immobilized in headrest and face mask and ready for a treatment.

Dosage.—Initially, the patient required only 2.7 mg/kg IM to produce a quiet, immobile state for the 5-minute sessions. After 5 treatments, this dosage proved inadequate and was increased to 3.6 mg/kg IM; while this was satisfactory for the next 21 sessions, an increase to 6 mg/kg IM was required for the final 3 sessions. Noteworthy was a change in anesthesiologists for these last 3 sessions.

Treatment and Recovery.—After injection in either buttock, the child remained in his mother's arms for the 2 to 4 minutes necessary to produce unconsciousness. He was then placed in the headrest, the face mask applied, and the radiation treatment begun. During the treatment, the patient was observed via closed-circuit television and directly through an observation port. Total time for treatment, from injection to the end of irradiation, averaged 10 to 11 minutes. The patient began to verbalize within 12 to 15 minutes from the time of injection and was fully recovered within 1 hour. He was able to leave the recovery area walking, escorted by his mother.

Complications.—Twice the patient produced copious secretions, necessitating suctioning and position changes; both episodes occurred in the afternoon after premedication with atropine. No treatments were prematurely terminated. Two sessions were interrupted to reposition the patient because of random hand motions and concluded without further incident. No postoperative complications, including bad dreams, hallucinations, emesis, or anorexia, were noted. Hemoglobin and WBC counts remained normal throughout the therapy, and no decrease in platelet count was observed. The patient's weight did not change over the 7-week course of treatment.

DISCUSSION

The anesthetic objectives for radiotherapy require rapid onset of action, brief duration, rapid recovery, preservation of protective reflexes with minimal cardiopulmonary depression, and good patient acceptance. We believe that ketamine fulfills these objectives better than any other drug or drug combination available.

Taylor and Towey[9] criticized the use of ketamine by demonstrating depression of the laryngeal closure reflex and radiographic evidence of aspiration under ketamine anesthesia. The dosages used, however, were not fully recorded. Dundee and Moore,[10]

using a small dose, were unable to substantiate Taylor's work. A later work by Carson and associates[11] showed frank aspiration in patients receiving 2 mg/kg IV but not in those whose dose was 1 mg/kg IV. In our patient, no signs or symptoms of aspiration or laryngospasm were observed.

Bad dreams or hallucinations have been associated with ketamine; however, this patient neither exhibited fear of the treatment nor did his mother relate any episodes of emergence complications.

One of the major disadvantages of repeated anesthetics is the disruption of eating patterns. Since the patient must, of necessity, be kept NPO prior to treatment, we chose 0900 hours as the optimal anesthetic time. Treatments were concluded by 0915 hours. By 1030 hours, the child was awake, hungry, and able to eat. He retained his appetite throughout the course of treatment, despite receiving 5600 rads and frequent anesthesia. The copious secretions noted on two occasions, when treatment was delayed until the afternoon, may have been secondary to increased anxiety and fasting, both of which contribute to an increase in salivation, aerophagia, and decreased gastric motility.[12]

Tachyphylaxis may have accounted for the increase in ketamine dosage from 3.6 to 6 mg/kg for the last 3 sessions; however, after 21 successful sessions using 3.6 mg/kg, the change in anesthesiologists seems a more likely cause. The rapport established between the patient and the primary anesthesiologist was lacking for the final 3 sessions, resulting in increased apprehension and anesthetic requirements. Anesthesiologists appreciate this correlation between reducing apprehension and subsequent anesthetic requirements, by conducting an informative preoperative visit.

REFERENCES

1. Harrison GG, Bennet MB: Radiotherapy without tears. Br J Anaesth 35:720-722, 1963

2. Browne CHW, Boulton TB, Erichton TC: Anaesthesia for radiotherapy. Anaesthesia 24:428-430, 1969

3. Bree MM, Feller I, Corssen G: Safety and tolerance of repeated anesthesia with CI 581 (ketamine) in monkeys. Anesth & Analg 46:596-600, 1967

4. Corssen G, Oget S: Dissociative anesthesia for the severely burned child. Anesth & Analg 50: 95-102, 1971

5. Sadove MS, Shulman M, Hatano S, et al: Analgesic effects of ketamine administered in subdissociative doses. Anesth & Analg 50:452-457, 1971

6. Cronin MM, Bousfield JD, Hewett EB, et al: Ketamine anaesthesia for radiotherapy in small children. Anaesthesia 27:135-142, 1972

7. Catton DV: Intramuscular ketamine-repeated injections. Can Anaesth Soc J 20:227-229, 1973

8. Piwoz S, Goldstein B: The use of ketamine anesthesia in radiation therapy. Radiology 109:725-726, 1973

9. Taylor PA, Towey RM: Depression of laryngeal reflexes during ketamine anaesthesia. Br Med J 2:688-689, 1971

10. Dundee JW, Moore J: Ketamine anaesthesia. Br Med J 3:46, 1971

11. Carson IW, Moore J, Balmer JP, et al: Laryngeal competence with ketamine and other drugs. Anesthesiology 38:128-133, 1973

12. Bogoch A: Gastroenterology. New York, McGraw-Hill Book Company, 1973, pp 12-13 and 22-24

INCIDENCE OF EXTRA-ARACHNOID CSF LEAKAGE AFTER LUMBAR PUNCTURE (German). In contrast-medium tests for postpunctural CSF leakage after lumbar puncture, comparison of 2 different needles in 100 myelographies showed a 1.2-mm OD needle to give nearly 300% more accurate findings than a 0.7-mm OD needle, using the same contrast medium (Dimer-X). Epidural leakage, the most frequent type, showed a "Christmas-tree" appearance on AP x-ray. Subdural leakage appeared in a "railroad-track" pattern on lateral viewing. *(Wiggli, Oberson. Schweiz Med Wochenschr 105:235-239, 1975.)*

N_2O Volumes Absorbed and Excreted During N_2O Anesthesia in Children

ERNEST SALANITRE, MD*
HERBERT RACKOW, MD†
New York, New York‡

Exhaled volumes were measured in 8 children during uptake and elimination of 3 percent and 75 percent N_2O, using a volume-controlled ventilator. Absorption of 75 percent N_2O during induction reduced the exhaled minute volume, which fell a mean of 16 percent in the 1st or 2nd minute and returned to normal by 15 to 20 minutes. Elimination was the mirror image of uptake; the mean increase in the exhaled minute volume was 13 percent. The concentration effect during uptake was measured (3 percent versus 75 percent N_2O) and the data were used to calculate a fall in alveolar volume of at least 8 percent by the 2nd minute of uptake. The type of ventilation (volume-limited, pressure-limited, or spontaneous) was seen to have a modifying role on the respiratory pattern caused by the absorbed and excreted volume of N_2O.

THE volume of gas absorbed into pulmonary capillary blood during N_2O anesthesia and then excreted into alveoli during elimination may cause such clinical conditions as diffusion anoxia[1] and the concentration effect.[2] Measuring volume and time course in 8 children, using a volume controlled ventilator, and ascertaining the concentration effect, previously reported only in dogs,[2,3] we used these data to calculate the reduction in alveolar volume (V_A) associated with the absorption of N_2O in clinical concentrations.

MATERIAL AND METHODS

Eight infants and children, 11 months to 6 years of age, were studied. All were without clinical evidence of cardiorespiratory disease. Data were obtained during the course of prolonged surgical procedures requiring many hours of anesthesia. Three patients underwent urethral operations, 4 had urinary bladder procedures, and one had rectal surgery.

Secobarbital, atropine, and, in one instance, meperidine were given for premedication. Induction of anesthesia was by face mask using halothane in O_2, except for an apprehensive child who received rectal sodium thiopental (25 mg/kg) followed by halothane and O_2 by mask. Succinylcholine (1 mg/kg) was administered intravenously prior to the insertion of a cuffed endotracheal tube. Air was injected into the cuff until no leakage could be heard from around the tube at an inflating pressure of about 20 torr. (This pressure was never exceeded by the inflating pressure of the respirator subsequently used.) Morphine and either d-tubocurarine or pancuronium were given intravenously, in repeated small doses, during the course of the anesthetic procedure, and ventilation was maintained with a volume-limited pediatric Frumin respirator

*Professor of Clinical Anesthesiology.
†Professor of Anesthesiology.
‡Department of Anesthesiology, College of Physicians and Surgeons, Columbia University; Anesthesiology Service, Presbyterian Hospital, New York, New York 10032.
This study was supported in part by NIH Grant GM 09069.
Paper received: 4/21/75
Accepted for publication: 5/6/75

and a nonrebreathing system. The halothane concentration was adjusted to 0.75 percent in O_2, and anesthesia and operation continued for at least 90 minutes before the studies began. In all cases, the studies were completed before the operation was terminated.

Vital signs were monitored with a chest or esophageal stethoscope, a standard blood-pressure cuff, ECG, and a rectal or esophageal temperature probe. Body temperature was kept between 36.5 and 37.5 C by controlling the temperature of the room and by a hot and cold circulating water mattress.*

An end-tidal sample of 0.75 ml was taken from the patient end of the endotracheal tube through a fine catheter, using an intermittent sampling pump automatically timed by the respirator to sample at the end of each expiration. This sample was pumped through the microcuvettes of three infrared analyzers† in series, one adjusted for N_2O concentrations between 0 and 4 percent, one for N_2O concentrations between 45 and 75 percent, and one for CO_2. The N_2O analyzer cases were filled with 100 percent CO_2 and the CO_2 analyzer case was filled with 100 percent N_2O, to eliminate "crossover" between the two gases.

The inspiratory tidal volume ($V_{T,I}$) was adjusted until the end-tidal CO_2 concentration stabilized at about 5 percent, then the respirator controls were not changed for the entire study. The rate of cycling was 24/min. The exhaled minute volume ($\dot{V}_E$) of all subjects was measured in a pair of "9" L lightweight spirometers counterbalanced on one chain and suspended in water. A double valve system allowed one spirometer to fill with the patient's expired air while the other was emptying into room air. When the first spirometer was filled, the valves were reversed. This system made it possible to use spirometers small enough to measure the $\dot{V}_E$ of an infant, and yet have the capacity to measure for several hours. A single kymograph recorded volumes. The end-tidal sample of 0.75 ml was neglected for volume measurements.

The constancy in the output of the ventilator (the inspired minute volume [$\dot{V}_I$]) was tested by connecting the ventilator through an appropriate resistance to the spirometers for 12 minutes and measuring low $\dot{V}_I$ by a pair of "1" L spirometers and measuring high $\dot{V}_I$ by the "9" L spirometers.

*Gorman-Rupp.

†Beckman Instrument, LB-1.

The halothane vaporizer was of the Copper Kettle® type, in which O_2 bubbled through liquid halothane. Its output was appropriately diluted with a separate flow of O_2 or N_2O-O_2, which resulted in a final concentration of 0.75 percent halothane. The temperature of the vaporizer remained constant throughout the period of the study.

Each patient was ventilated initially with an inspired gas mixture of 0.75 percent halothane in O_2. After pulse, blood pressure, body temperature, end-tidal CO_2 concentration, and $\dot{V}_E$ were stable during a first control period of 10 to 20 minutes, the diluent gas was changed abruptly‡ from 100 percent O_2 to approximately 3 percent N_2O in O_2, premixed in a tank, for the first uptake study. Following 15 to 20 minutes of N_2O uptake, the diluent gas was abruptly changed back again to 100 percent O_2 for the first elimination study. End-tidal N_2O, end-tidal CO_2, and $\dot{V}_E$ were measured during both the uptake and elimination phases of the 3 percent N_2O study.

The second control period began when end-tidal N_2O concentration fell to less than 0.05 percent during the elimination phase, with 100 percent O_2 as the diluent. The same sequence was repeated, using 75 percent instead of 3 percent premixed N_2O-O_2. Similar volume measurements were made but end-tidal N_2O concentration was not monitored during elimination of 75 percent N_2O, (as the high-concentration N_2O analyzer was internally adjusted with a suppressed zero at 45 percent N_2O to attain the desired sensitivity for the uptake study).

The sampling, analytical, and recording systems have been previously described.[3] At frequent periods during each study, inspiratory gas mixture was analyzed and the infrared analyzers were calibrated against known gas concentrations delivered from previously analyzed premixed tanks.

Pulmonary equilibration curves were constructed for the uptake period of N_2O by converting the end-tidal N_2O concentrations to F_E/F_I ratios (end-tidal concentration/inspired concentration) and plotting them against time.

‡The internal volume of the respirator (estimate, 200 ml) could not be emptied and refilled instantaneously at time zero. This created an error with a time constant calculated to be about 0.14 minutes for the smallest patient whose $\dot{V}$min was 1455 ml/min (time constant, assuming $\dot{V}_I = \dot{V}_E$, = vol/flow = 200 ml/1455 ml/min = 0.14 min). The error is the same for the two concentrations of N_2O used and in any event becomes insignificant in about ½ minute.

TABLE

Maximum Change in Exhaled Minute Volume ($\dot{V}_E$) During Uptake and Elimination of 75 Percent N_2O

Patient number	Age	Weight, kg	Control $\dot{V}_E$ 3% N_2O, ml/min	Control $\dot{V}_E$ 75% N_2O, ml/min	Uptake change, %	Elimination change, %
1	11 mo	7.4	1455	1456	−13.9	+13.2
2	19 mo	8.5	1380	1428	−16.8	+11.4
3	2½ yr	13.9	1970	2059	−16.2	+8.7
4	3 yr	14.5	2179	2201	−16.6	+12.2
5	3 yr	14.6	2345	2304	−15.6	—
6	3 yr	20.0	2568	2592	−15.7	+12.2
7	5 yr	19.8	2575	2632	−17.6	—
8	6 yr	19.5	2400	2376	−17.1	+20.2
				Mean change (± SD)	−16.2 ± 1.3	+13.0 ± 4.1

RESULTS

1. Variations in the $\dot{V}_I$.—The output of the Frumin pediatric respirator ($\dot{V}_I$), as measured in each of a pair of "1" L spirometers for 12 minutes at a low V_T averaged 1377 ml ± 7.4 ml (SD) and 1315 ml ± 17 ml. As measured in each of the pair of "9" L spirometers at a higher V_T the minute output of the respirator averaged 9964 ml ± 31 ml and 10,081 ml ± 45 ml. The SD was about ± 1 percent of the $\dot{V}$min at low V_T and less at higher V_T. The pair of "1" L spirometers differed by 5 percent, while the "9" L spirometers differed by 1 percent.

2. Exhaled $\dot{V}$min During Control Periods.—During the first and second control periods in patient 1 (table) $\dot{V}_E$ was 1455 ml ± 28 ml and 1456 ml ± 21 ml, respectively. The SD was less than ± 2 percent of the $\dot{V}_E$. The control $\dot{V}_E$ of all patients is shown in the table.

3. Exhaled $\dot{V}$min During 3 Percent N_2O Uptake.—$\dot{V}_E$ in patient 1 (table) averaged 1461 ml ± 19 ml. These data are not significantly different by Student's *t*-test from the $\dot{V}_E$ during the first control period. The same pattern was found in the other subjects (table).

4. Exhaled $\dot{V}$min During 75 Percent N_2O Uptake.—This fell in the 1st minute in patient 1 from an average of 1456 to 1253 ml and then gradually returned to control by 20 minutes, a fall of 203 ml, or −13.9 percent of control. The difference from control for the first 10 minutes was −795 ml or −5.5 percent of the total control exhaled volume. The maximum change in $\dot{V}_E$ for each subject occurred in either the 1st or 2nd minute of uptake (table), for a mean value of −16.2 ± 1.3 percent.

5. Exhaled $\dot{V}$min During Elimination of 75 Percent N_2O.—$\dot{V}_E$ during elimination increased to 1649 ml in patient 1 in the 1st minute and then gradually returned to control by 15 minutes, a rise of 193 ml or +13.2 percent of control (fig 1). The $\triangle\dot{V}_E$ in the 1st 10 minutes was +773 ml or +5.3 percent of control. Mean change at the peak effect for all subjects was +13.0 ± 4.1 percent and occurred in either the 1st or 2nd minute of elimination (table).

6. Pulmonary Equilibration of 3 Percent N_2O and 75 Percent N_2O During Uptake.—The pulmonary equilibration curve (end-tidal N_2O/inspiratory N_2O, F_E/F_I, versus time) for 75 percent N_2O for subject 1 is

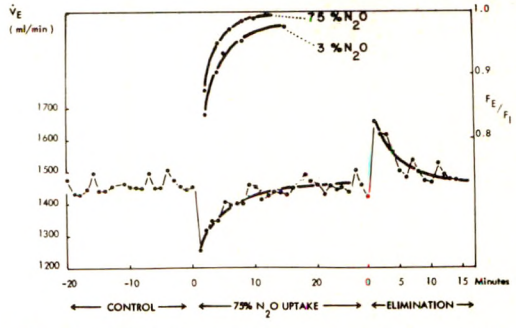


FIG 1. Exhaled minute vol ($\dot{V}_E$) during uptake and elimination of 75% N_2O, and the concentration effect. (3% versus 75% N_2O) in an 11-month-old infant.

shown in figure 1, with the 3 percent N_2O equilibration curve for comparison. The 75 percent curve is closer to inspiratory tension than the 3 percent. This same pattern was seen in each subject. The average 3 percent and 75 percent curves for all subjects and the range are shown in figure 2. The difference in F_E/F_I between the 3 and 75 percent curves is 0.07 at 2 minutes, 0.06 at 5 minutes, and 0.05 at 10 minutes.

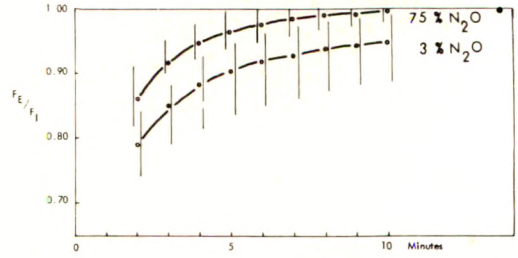


FIG 2. Concentration effect in 8 children. Circles indicate means; bars indicate range. F_E/F_I =-end-tidal concentration/inspired concentration ratio.

DISCUSSION

Uptake of 3 percent N_2O had an insignificant effect on the $\dot{V}_E$, since the volume of N_2O exchanged was small. However, the uptake of 75 percent N_2O caused a fall and then, during elimination, a rise in $\dot{V}_E$. This is a measure of the magnitude and time course of the absorbed and then excreted volume of N_2O (fig 1 and table). The size and the time course of the absorbed volume were the inverse of those of the excreted volume, but otherwise were similar. This follows the expected course of N_2O absorption and excretion and corresponds well with the calculated[4,5] and measured time course of exchange of N_2O between lung and pulmonary capillary blood in adults.[6]

The magnitude of the effect of absorption of N_2O on exhaled $\dot{V}$min can be calculated. In subject 1, the $\dot{V}_E$ fell 203 ml in the 1st minute (fig 1), or −13.9 percent of control. The average volume of N_2O absorbed per breath during the 1st minute was 13.9 percent × the control V_T of 60.6 ml, or 8.5 ml. In this 1st minute, the maximum absorbed volume in a single breath must have been higher than the average, 8.5 ml, since at time zero, absorption was zero, and then gradually reached a maximum. The mean change in the $\dot{V}_E$ at the peak effect for all subjects was −16.2 percent during uptake and +13.0 percent during elimination (table). For comparison, in the resting steady state in the infant and adult, the volume of O_2 absorbed is 4 to 5 percent of the $\dot{V}$min,[7,8] and most of this absorption effect is counterbalanced by simultaneous excretion of CO_2.

The maximum effect of absorption of N_2O on lung volume is also of interest and may be calculated from figure 2, which shows the average concentration effect for all subjects during uptake. It is important to remember that during uptake with a volume-controlled ventilator, absorption of N_2O reduces lung volume as it changes during the breathing cycle. This increases the tension of all alveolar gases, compared to what the tension would have been without any shrinking of lung volume. The magnitude of this concentration effect (3 percent versus 75 percent N_2O) at the end of the first 2 minutes can be estimated as follows:

1. At 2 minutes, for 3% N_2O,
$$\frac{F_E}{F_I} = \frac{2.49\% \text{ (measured)}}{3.15\% \text{ (inspired)}} = 0.79$$
2. At 2 minutes, for 75% N_2O,
$$\frac{F_E}{F_I} = \frac{64.5\% \text{ (measured)}}{75.3\% \text{ (inspired)}} = 0.86$$

3. If there were no shrinkage of lung volume, F_E/F_I for 75 percent N_2O would theoretically be the same as that for 3 percent N_2O (0.79) and the theoretic alveolar N_2O concentration would be 59.4 percent instead of 64.5 percent:
$$\frac{F_E}{F_I} = \frac{59.4\% \text{ (theoretic)}}{75.3\% \text{ (inspired)}} = 0.79$$

The amount of lung volume shrinkage necessary to increase this theoretic 59.4 percent N_2O to the measured 64.5 percent is:

$$\frac{59.4 \text{ ml } N_2O}{100 \text{ ml lung vol}} \xrightarrow{\text{shrinkage of lung}} \frac{59.4 \text{ ml } N_2O}{x \text{ ml lung vol}}$$

$$= 64.5\% \ N_2O. \quad x \text{ ml lung vol} = \frac{59.4 \text{ ml}}{64.5\%} = 92 \text{ ml}$$

Thus, the shrinking of lung volume was 8 percent. This represents an average change over the first 2 minutes and is an approximation only, since the increased tension due to the shrinkage must have caused further absorption of the 59.4 ml of N_2O, which in turn would cause further shrinkage of the 92 ml of lung volume. All alveolar gases (O_2, CO_2, halothane) in addition to N_2O, are affected.[3,4,9,10]

The effect on the respiratory pattern due to the absorbed and excreted volume of N_2O will vary according to the type of ventilation.[11] During uptake, absorption causes

spontaneous respiration (at constant P_{CO_2}) to have the largest inspired and expired V_T compared with other types of ventilation. A volume-limited ventilator will have the smallest inspired and expired V_T, while a pressure-limited ventilator will be in between. During elimination, excretion causes the reverse order. Since our data on the concentration effect during uptake were obtained with a volume-limited ventilator, they represent a smaller effect than would be seen with other types of ventilation.

In the first description of pulmonary absorption-excretion volume effects, Fink[1] also measured $\dot{V}$min, estimating the eliminated N_2O as being 10 to 12 percent of the total exhaled volume in the first 10 minutes during recovery from N_2O anesthesia. This is about twice the value we obtained in the same 10 minutes, but use of a volume-limited ventilator should show a smaller effect. However, unlike our study, the time course of the eliminated N_2O in Fink's study did not follow a consistent pattern of excretion: in one of the three patients whose inspired and expired volumes were studied, the exhaled $\dot{V}$min gradually increased in the first 10 minutes, reaching a peak at the end; in the second, it promptly reached a peak and then gradually decreased; and in the third, it immediately reached a plateau which was relatively stable for the entire period. These were spontaneously breathing surgical patients recovering from anesthesia. They must have experienced changing levels of anesthesia and pain, even though breathing was regular. This may have contributed to variations in ventilation and circulation that could explain the inconsistent time course.[4]

Sheffer's group[6] also studied diffusion anoxia in spontaneously breathing adults, noting a fall in P_{aCO_2} of about 10 torr which persisted after N_2O excretion had fallen. A sustained fall in P_{aCO_2} in the presence of an ever-decreasing excretion of N_2O can be explained only by a sustained increase in the inspired V_T (causing a similar increase in the expired V_T) and/or a persistent fall in CO_2 transport to the lungs. Although these variations in ventilation and circulation are the true clinical conditions of recovery, they modify the time course of elimination of N_2O and make difficult the study of the basic effect of volume change alone.

In our studies with children, during the periods of uptake and elimination of 75 percent N_2O, the higher concentration could have affected cardiac output even though no changes in pulse and blood pressure were seen. An increase in cardiac output would increase the pulmonary absorbed/excreted volume of N_2O/min and increase the concentration effect, while a decrease in cardiac output would do the reverse. However, Smith and coworkers[12] found that, in healthy adults during steady state, light halothane anesthesia, 0.8 to 1.2 percent end-tidal, with controlled ventilation and no surgical operation, there was no change in cardiac output, pulse, or blood pressure upon addition of 70 percent N_2O. Our conditions were similar though not identical.

REFERENCES

1. Fink BR: Diffusion anoxia. Anesthesiology 16:511-519, 1955

2. Eger EI II: Effect of inspired anesthetic concentration on the rate of rise of alveolar concentrations. Anesthesiology 24:153-157, 1963

3. Epstein RM, Rackow H, Salanitre E, et al: Influence of the concentration effect on uptake of anesthetic mixtures: the second gas effect. Anesthesiology 25:364-371, 1964

4. Rackow H, Salanitre E, Frumin MJ: Dilution of alveolar gases during nitrous oxide anesthesia in man. J Appl Physiol 16:723-728, 1961

5. Perl W: Uptake and Distribution of Anesthetic Agents, Edited by EM Papper, R Kitz. New York, McGraw-Hill Book Company, Inc, 1963, Chapter 19, pp 250-257

6. Sheffer L, Steffenson JL, Birch AA: Nitrous oxide induced diffusion hypoxia in patients breathing spontaneously. Anesthesiology 37:436-439, 1972

7. Gray JS: Pulmonary ventilation and its physiological regulation, American Lecture Series No. 63. Springfield, Illinois, Charles C Thomas, Publisher, 1950

8. Cross KW, Tizard JPM, Trythall DAH: The gaseous metabolism of the newborn infant. Acta Paediat 46:265-285, 1957

9. Heller ML, Watson TR: The role of preliminary oxygenation prior to induction with high nitrous oxide mixtures. Polarographic P_{ao_2} studies. Anesthesiology 23:219-230, 1962

10. Kitahata LM, Taub A, Conte AJ: The effect of N_2O on alveolar CO_2 tension: a second gas effect. Anesthesiology 35:607-611, 1971

11. Salanitre E, Rackow H: Recent advances in uptake and excretion of inhalation anesthetics, A Decade of Clinical Progress. Edited by LW Fabian. Philadelphia, FA Davis Company, 1971, Clinical Anesthesia, chapter 7

12. Smith NT, Eger EI II, Stoelting R, et al: The cardiovascular and sympathomimetic responses to the addition of nitrous oxide to halothane in man. Anesthesiology 32:410-421, 1970

Absence of Autoregulation of Cerebral Blood Flow During Halothane and Enflurane Anesthesia

DAVID J. MILETICH, PhD*
ANTHONY D. IVANKOVICH, MD†
RONALD F. ALBRECHT, MD‡
CHARLES R. REIMANN, MD§
RONALD ROSENBERG, MD‖
EVERETT D. McKISSIC, MD**
Chicago, Illinois††

The effects of halothane and enflurane anesthesia under conditions of normo-, hyper-, and hypocarbia on the autoregulation of cerebral blood flow (CBF) in the goat were evaluated. The goat was selected because of its unique arterial blood supply to the head and the development of a method by which CBF may be continuously measured. The study revealed that 1 MAC of halothane or enflurane anesthesia at normocarbia abolished cerebral autoregulation, CBF increasing or decreasing with increasing or decreasing peripheral blood pressure. Reduction of anesthesia to 0.5 MAC partially restored cerebral autoregulatory capability. The effect of 1 MAC and 0.5 MAC anesthesia on cerebral autoregulation of blood flow was potentiated by hypercarbia and antagonized by hypocarbia, indicating that the vascular response to blood CO_2 fluctuations remained intact.

IT IS generally presumed that halogenated hydrocarbon anesthetics have little effect on the cerebral vascular autoregulatory mechanism, despite ample demonstration that these agents are potent cerebral vasodilators.[1-6] Severe technical restraints in studying moment-to-moment cerebral blood flow (CBF) exclusive of changes in peripheral hemodynamics have no doubt confounded separation of the direct vascular action of anesthetics from their effects on cerebral regulatory mechanisms.

In this study, the effects of halothane and enflurane anesthesia under conditions of hyper-, normo-, and hypocarbia on the autoregulation of CBF in the goat were evaluated. The goat was chosen because of its unique arterial blood supply to the head and the development of a method by which CBF may be continuously measured in both anesthetized and unanesthetized animals.[7,8]

METHODS

The studies were performed on a model developed by Reimann's group[7] for the continuous measurement of ipsilateral CBF in the unanesthetized, unrestrained goat. Full anatomic descriptions of the arterial blood

*Assistant Professor of Anesthesiology, Pritzker School of Medicine, The University of Chicago.

†Associate Professor of Anesthesiology, Pritzker School of Medicine, The University of Chicago.

‡Professor of Anesthesiology, Pritzker School of Medicine, The University of Chicago; Chairman, Department of Anesthesiology, Michael Reese Medical Center.

§Research Associate, Department of Anesthesiology, Michael Reese Medical Center.

‖Associate Professor of Anesthesiology, Pritzker School of Medicine, The University of Chicago.

**Assistant Professor of Anesthesiology, Pritzker School of Medicine, The University of Chicago.

††Department of Anesthesiology, Michael Reese Medical Center, Chicago, Illinois 60616.

Read at the 49th Congress of the International Anesthesia Research Society, March 16-20, 1975, Hollywood, Florida.

Paper received: 3/17/75
Accepted for publication: 7/30/75

supply to the goat brain and the detailed methods employed to prepare the animal for study have been presented elsewhere.[9,10] Briefly, total blood flow to each cerebral hemisphere is provided by a single external carotid artery. The external carotid bifurcates extracranially, forming the lingual and internal maxillary arteries. Two major vessels, the ramus anastomoticus and arteria anastomotica, arise from the internal maxillary and enter the cranial vault where they empty into the rete mirabile. The rete mirabile consists of a compact network of intertwined, freely anastomosing arteries permitting a high degree of contralateral communication across the midline of the brain and rete. The vascular communication is so extensive that the two structures are virtually one. Blood leaves the rete by the right and left internal carotid arteries and empties into the circle of Willis. Branches from the internal maxillary also supply blood to the extracerebral tissues via the buccinator, ethmoidal, and ophthalmic arteries.

Eight mature female goats weighing 30 to 40 kg were surgically prepared for study as follows: Anesthesia was induced with mask-administered halothane, after which the animal was intubated; artificial respiration was maintained using an Ohio respirator with 1.5% halothane in 100% O_2. An esophageal gastric tube was inserted to prevent vomiting and aspiration. A lateral incision was made along either the right or left mandible and a small portion of the mandible was removed to expose the internal maxillary, ramus anastomoticus, temporal, and dental arteries. Ligatures were placed around the internal maxillary distal to the ramus anastomoticus and on the temporal and dental arteries.

Due to their physical inaccessibility, extracerebral blood flow through the ophthalmic, ethmoidal, and buccinator arteries was obliterated by slowly injecting 1 to 2000 NIH units of thrombin in 0.5 ml of saline solution into the internal maxillary artery anterior to the site of ligation. The injected thrombin produced immediate clotting and elimination of extracerebral blood flow, as evidenced by the appearance of thrombosed vessels in the sclera and postsurgical ipsilateral blindness.

After this, a 4-mm Statham electromagnetic flow probe was placed around the internal maxillary artery for the continuous measurement of ipsilateral cerebral blood flow. A left thoracotomy was also performed and an 18-mm Statham electromagnetic flow probe was placed around the pulmonary artery for the measurement of cardiac output. A long, firm catheter was introduced into the aorta through the femoral artery for blood-gas and arterial blood pressure measurements. A similar catheter was placed in the femoral vein for the infusion of pressor drugs. All incision sites were appropriately closed for proper healing. In most cases, the animals were ready for study 2 weeks after the surgical procedures.

The presence or absence of autoregulation of CBF in the experimental animals was determined by simply increasing or decreasing systemic arterial pressure through the infusion of vasoactive agents while simultaneously monitoring CBF. In the awake animal, angiotension and/or dopamine was infused via the femoral vein catheter with a constant-rate infusion pump in sufficient concentrations to raise arterial pressure. (Neither agent separately nor in combination had any effect on CBF in the awake animal.) Sodium nitroprusside was used to lower arterial pressure. In animals anesthetized with halothane or enflurane, hypotension was produced as a consequence of the anesthetic and it was therefore only necessary to raise arterial pressure by infusing angiotensin or dopamine to verify the presense or absence of cerebral autoregulation.

Conditions of hypercarbia in anesthetized animals was produced by having the animals breathe a mixture of 10% CO_2 and air. Hypocarbia was produced by hyperventilation. Blood samples were drawn at appropriate times throughout each experiment for blood-gas analysis and gas chromatographic analysis of anesthetic concentration.

Eight animals were randomly studied under the following experimental conditions: awake; 0.5 MAC halothane anesthesia at hyper-, hypo-, and normocarbia; 1 MAC halothane anesthesia at hyper-, hypo-, and normocarbia. Six animals were studied as described but with enflurane. N_2O was not used in any of the experimental trials involving 1 MAC anesthesia and was used only when necessary during 0.5 MAC anesthesia. O_2 (100%) was used at all experimental trials except with awake animals.

RESULTS

CBF remained remarkably constant throughout an increase or decrease in MAP between 60 to 200 torr in the awake animal

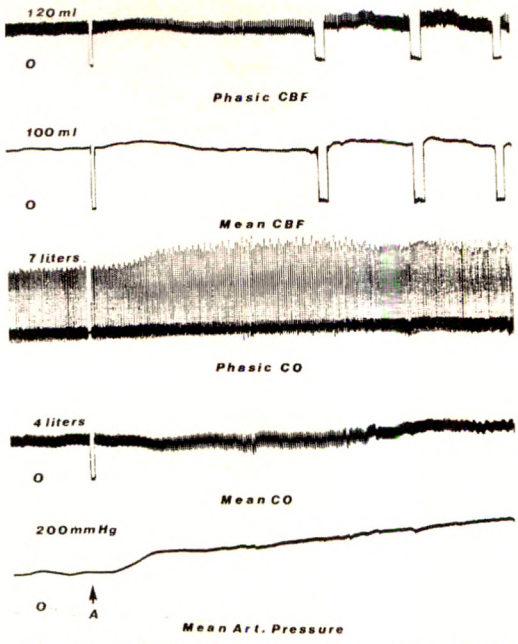


FIG 1. Effects of increasing systemic arterial pressure on ipsilateral CBF in the awake goat. Elevation in MAP to 200 torr produced only a slight increase in CBF. CBF = cerebral blood flow in ml/min; CO = cardiac output in L/min. Recording paper speed 1 mm/sec.

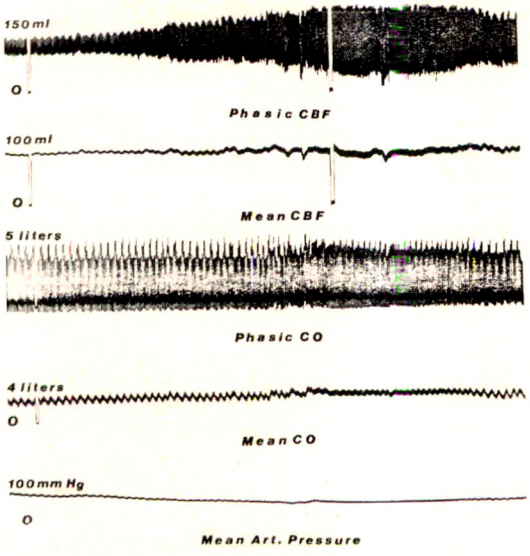


FIG 2. Effects of decreasing systemic MAP on ipsilateral CBF in the awake goat. Decreases in MAP to 50 torr produced only a slight decrease in CBF. Recording paper speed 1 mm/sec.

(fig 1 and 2). However, during 1 MAC halothane anesthesia (fig 3) under normo-, hyper-, and hypocarbia, autoregulation of CBF was abolished. With each progressive

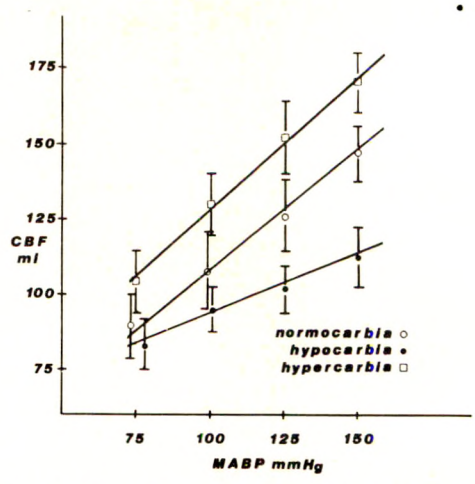


FIG 3. Effects of increasing systemic MABP on ipsilateral CBF during 1 MAC halothane anesthesia (average) 17 ± 5.6 mg/100 ml blood ± SD, n = 8) at normocarbia (average Pco_2 32.7 ± 6.2 ± SD, n = 8), hypercarbia (average Pco_2 68 ± 10.4 ± SD, n =8), and hypocarbia (average Pco_2 19.3 ± 2.6 ± SD, n = 8).

increase in MAP, there was a parallel elevation in CBF (fig 4). Compared with normocarbia, hypocarbia reduced both the magnitude and rate of change in cerebral flow. Hypercarbia increased the magnitude of CBF but did not affect the rate of change of cerebral flow. Enflurane, in equipotent anesthetic concentrations, produced similar effects on autoregulation as compared to halothane (fig 5).

Reduction of halothane anesthetic levels to approximately 0.5 MAC partially restored autoregulation of CBF. At normal blood

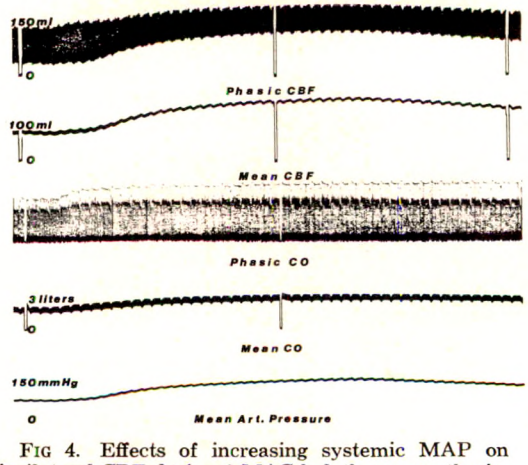


FIG 4. Effects of increasing systemic MAP on ipsilateral CBF during 1 MAC halothane anesthesia. Recording paper speed 1 mm/sec.

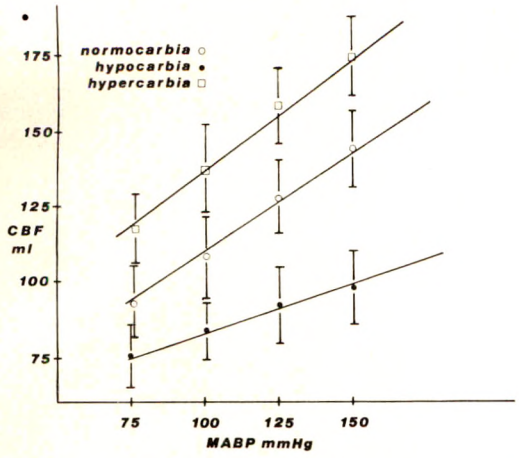


FIG 5. Effects of increasing systemic MABP on ipsilateral CBF during 1 MAC enflurane anesthesia (average 26.2 ± 8 mg/100 ml blood ± SD, n = 6) at normocarbia (average Pco_2 34.2 ± 2.3 ± SD, n = 6), hypercarbia (average Pco_2 59.1 ± 7.7 ± SD, n = 6), and hypocarbia (average Pco_2 22 ± 6.3 ± SD, n = 6).

CO_2 concentrations, CBF increased with increasing blood pressure up to a MAP of about 96 torr (fig 6). After this, CBF no longer increased, despite continued elevation in arterial blood pressure (fig 7). Presumably, the pressure at which CBF leveled off is the point in arterial pressure at which autoregulation of cerebral flow became manifest. Hypocarbia slightly reduced the "autoregulatory point" in arterial pressure, while hypercarbia elevated the autoregulatory point (fig 6).

The susceptibility of CBF to sudden changes in peripheral hemodynamics in the absence of autoregulation due to 1 MAC halothane anesthesia can be seen in figure 8.

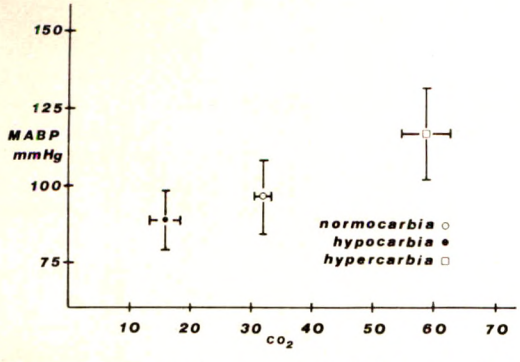


FIG 6. The point in systemic MABP above which the autoregulation of CBF became manifest during 0.5 MAC halothane anesthesia (average 8.45 ± 2.3 mg/100 ml blood, n = 8) at normo-, hyper-, and hypocarbia.

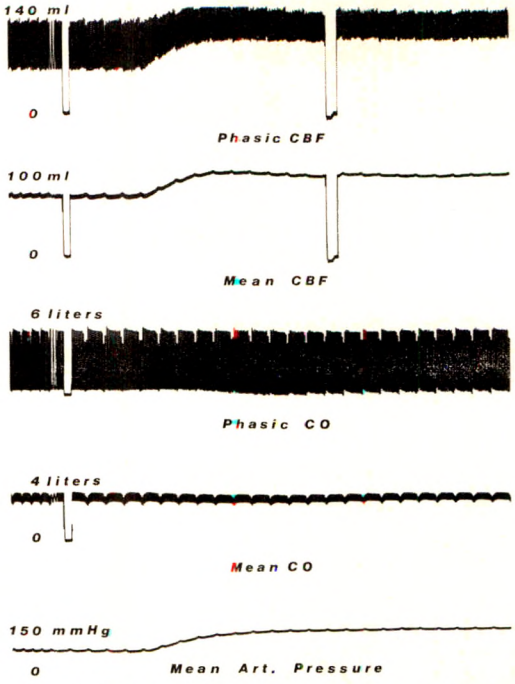


FIG 7. Effects of increasing systemic MAP on ipsilateral CBF during 0.5 MAC halothane anesthesia. Recording paper speed 1 mm/sec.

A spontaneous episode of decreased cardiac output and blood pressure was immediately reflected in CBF.

Figure 9 illustrates an atypical CBF response to blood pressure change (as compared to the typical, in fig 7) under 0.5

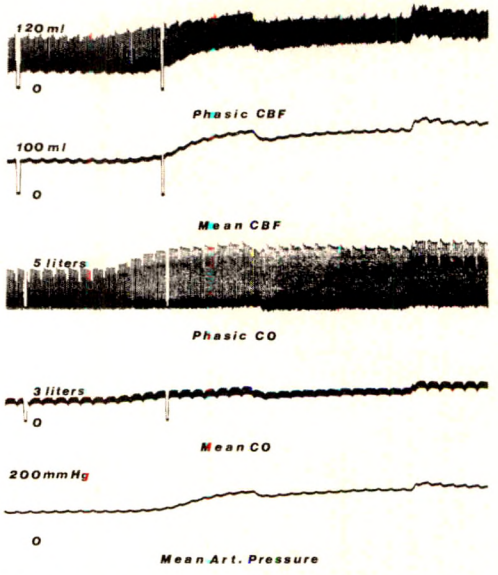


FIG 8. Demonstration of the susceptibility of CBF to sudden changes in peripheral hemodynamics during 1 MAC halothane anesthesia at normocarbia. Recording paper speed 1 mm/sec.

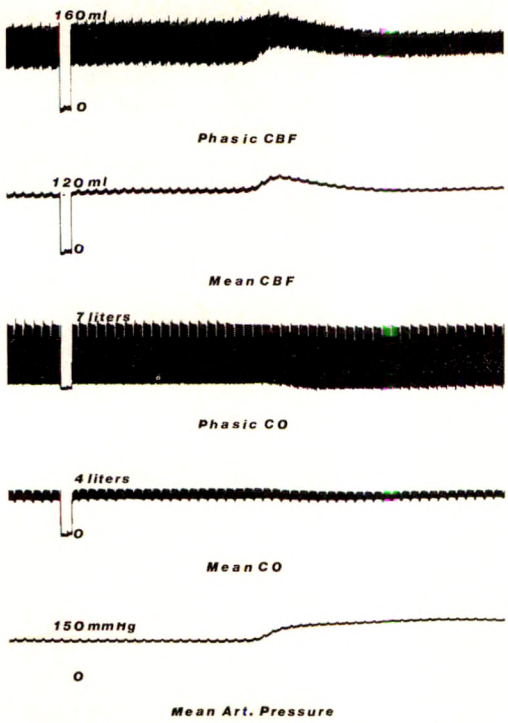


FIG 9. Demonstration of partially impaired autoregulation of CBF during 0.5 MAC halothane anesthesia shortly after induction of anesthesia. Recording paper speed 1 mm/sec.

MAC halothane anesthesia at normocarbia. In this situation, CBF returned to preangiotensin levels, while arterial pressure remained elevated. This kind of response was generally seen shortly after the induction of anesthesia and was usually not demonstrable after approximately 20 minutes of anesthesia. Presumably, in the early phase of anesthesia, the brain and vascular tissues had not equilibrated in terms of anesthetic concentration with the blood and therefore retained some autoregulatory capability.

DISCUSSION

Autoregulation of CBF may be described as the ability of the brain to maintain an adequate flow consistent with its metabolic needs, independent of changes in peripheral hemodynamics. Ordinarily, in many species, of animals and man, changes in MAP, between 60 and 150 torr, have little effect on CBF[11,12] However, the goat has a greater autoregulatory range, and MAP changes up to 200 torr produced little effect on the magnitude of CBF (fig 1). The ability of the goat to maintain a constant cerebral flow at extremely high arterial pressures is due to the rete mirabile being distal to the circle of Willis, where it damps excessively high peripheral arterial pressures but has little effect on pressures between 50 and 150 torr.[13]

As seen in this study, halothane and enflurane anesthesia impair the cerebral autoregulatory mechanism. Light anesthesia, eg, 0.5 MAC, at normocarbia reduces the effective range of MAP over which CBF is regulated (fig 6 and 7). Up to a mean pressure of 96 torr, CBF passively follows peripheral changes in pressure. Above 96 torr, autoregulatory capability appears intact, since CBF exhibits no further increase despite continued elevation in peripheral pressure. Increasing the depth of anesthesia to 1 MAC at normocarbia totally eliminates effective cerebral autoregulation (fig 3, 4, and 5). CBF increases linearly with increases in MAP from 60 through 150 torr.

CO_2, the most potent cerebral vasodilator known, is reportedly[2,14] potentiated by halothane anesthesia. However, it is not clear from these reports whether the observed halothane-CO_2 "potentiation" was simply addition of their vasodilative effects or true potentiation (which would require that the two in combination produce a greater effect than the sum of their individual effects). In the present study, the problem of halothane-CO_2 "potentiation" could not be resolved, but it was evident that the level of blood CO_2 had considerable impact on the state of cerebral autoregulation during anesthesia. The effect of CO_2 was best seen in situations of 0.5 MAC anesthesia (fig 6).

Hypocarbia enlarged the range of arterial pressure over which CBF was regulated as compared with normocarbia, while hypercarbia reduced the range. Since decreased CO_2 decreased the point in peripheral pressure at which autoregulation began, while increased CO_2 increased that point, it would appear that the vascular effects of CO_2 were merely superimposed on the anesthetic effect. This likelihood was further substantiated by the demonstration that elevated blood CO_2 during 1 MAC anesthesia increased the magnitude of CBF, but did not alter the rate of CBF increase. However, hypocarbia not only reduced the magnitude of CBF but significantly lessened the rate of cerebral flow increase (fig 3 and 4). The latter observation would imply that the vasoconstrictive effect of hypocarbia predominates over the vasodilative effects of halothane or enflurane anesthesia.

These findings suggest that, independent of other considerations, hypocarbia would be a desirable adjunct to anesthetic management involving patient requiring positional changes.

Most attempts to explain the mechanism of CBF autoregulation fall into one of 3 hypotheses: (1) the vasomotor theory,[15] (2) the metabolic theory,[16] or (3) the neurologic reflex theory.[17,18] All three explanations lack definitive experimental evidence and are based primarily on inference. Evidence for a neurologic reflex mechanism in the control of CBF is of such an indirect nature that it is difficult to accept. The metabolic theory proposes that a rapid build-up of acid metabolites induces vascular vasodilation, but the mechanism of cerebral vascular vasoconstriction in response to peripheral pressure increases is not as easily explained and is therefore a major weakness in this theory. The vasomotor theory is perhaps the most logical and is thus the most generally accepted.

Simply stated, the vasomotor theory requires that the smooth muscle layer of the cerebral vessels act as stretch receptors atuned to the state of intraluminal pressure. As intraluminal pressure increases, the smooth muscle layer contracts and as pressure drops, the smooth muscle relaxes. While the idea appears plausible, the present study would indicate that refinement of this concept is necessary to comply with experimental observation.

As demonstrated, 1 MAC of halothane or enflurane anesthesia abolishes autoregulation, suggesting relaxation and/or paralysis of cerebrovascular smooth muscle. However, since the cerebral vessels retained the ability to respond to changes in blood CO_2 levels during 1 MAC anesthesia, relaxation or paralysis of vascular smooth muscle would seem unlikely as an explanation for the loss of autoregulation. It is apparent that the cerebrovascular response to systemic arterial-pressure fluctuations and blood CO_2 changes are initiated by separate, specific pathways but are manifested by the same mechanism, the contraction or relaxation of vascular smooth muscle.

Specificity suggests the presence of discrete receptors or mechanisms for both physiologic responses. Within the autoregulatory pathways, these receptors apparently are not homogenous, or they are physically distributed in such a way as to render some of them less accessible to anesthetic interaction than others. The response seen in figure 9 could be explained by a receptor fitting this description. (It should be understood that the term "receptor" as used here refers to either a specific molecular configuration or a particular metabolic event which, when appropriately agonized, would lead to vascular smooth muscle activity.) The change in CBF following an increase in arterial blood pressure during 0.5 MAC halothane anesthesia at normocarbia (fig 9) was only seen shortly after the induction of anesthesia and presumably represents a situation in which the cerebral vascular and brain tissue had not been completely saturated with anesthetic, thus retaining some autoregulatory capability. Clearly, then, the autoregulation of CBF is not an "all-or-none" process. Partially impaired autoregulation of CBF has also been reported in situations of brain injury[19] and hypoxia.[20]

Earlier reports[14,21] have asserted that halothane anesthesia does not disrupt cerebral autoregulation. These assertions were based on static hemodynamic observations. A single measurement of CBF at any particular peripheral arterial pressure gives no information concerning the status of cerebral autoregulation. Assessment of the integrity of autoregulation during anesthesia requires multiple CBF measurements as peripheral pressure changes.

ACKNOWLEDGMENT

The authors extend their gratitude to Mss C. Seals and A. Jozefiak and to Mr. D. Visintine for exceptional technical assistance.

REFERENCES

1. McDowall DG: The effects of clinical concentrations of halothane on the blood flow and oxygen uptake of the cerebral cortex. Br J Anaesth 39:186-196, 1967

2. Christensen MS, Hoedt-Rasmussen K, Lassen NA: Cerebral vasodilatation by halothane anaesthesia in man and its potentiation by hypotension and hypercapnia. Br J Anaesth 39:927-934, 1967

3. Wollman H, Alexander SC, Cohen PJ, et al: Cerebral circulation of man during halothane anesthesia—the effects of hypocarbia and d-tubocurarine. Anesthesiology 25:180-184, 1964

4. Smith AL, Neigh JL, Hoffman C, et al: Effects of general anesthesia on autoregulation of cerebral blood flow in man. J Appl Physiol 29:665-669, 1970

5. Smith AL, Wollman H: Cerebral blood flow and metabolism: effects of anesthetic drugs and techniques. Anesthesiology 36:378-400, 1972

6. Michenfelder JD, Theye RA: Effects of methoxyflurane on canine cerebral metabolism and blood flow. Anesthesiology 38:123-127, 1973

7. Reimann C, Lluch S, Glick G: Development and evaluation of an experimental model for the study of the cerebral circulation in the unanesthetized goat. Stroke 3:322-328, 1972

8. Miletich DJ, Ivankovich AD, Albrecht RF, et al: Cerebral hemodynamics following internal maxillary artery ligation in the goat. J Appl Physiol 38:942-945, 1975

9. Andersson B, Jewell PA: The distribution of carotid and vertebral blood in the brain and spinal cord of the goat. Q J Exp Physiol 41:462-474, 1956

10. Ivankovich AD, Miletich DJ, Reimann C, et al: Cardiovascular effects of centrally administered ketamine in goats. Anesth & Analg 53:924-933, 1974

11. Harper AM, Lassen NA, MacKenzie EF: The upper limit of autoregulation of cerebral blood flow in the baboon. Physiol Soc 234:61P-62P, 1973

12. Lassen NA: Cerebral blood flow and oxygen consumption in man. Physiol Rev 39:183-238, 1959

13. Edelman NH, Epstein NS, Cherniak N: Control of cerebral blood flow in the goat; role of the carotid rete. Am J Physiol 223:615-619, 1972

14. Alexander SC, Wollman H, Cohen PJ, et al: Cerebral vascular response to $Paco_2$ during halothane anesthesia in man. J Appl Physiol 19:561-565, 1964

15. Symon L, Held K, Dorsch WC: On the myogenic nature of the autoregulatory mechanism in the cerebral circulation. Eur Neurol 6:11-18, 1971

16. Betz E: The significance of cortical extracellular pH for the regulation of cerebral blood flow in the cerebral cortex. Prog Brain Res 30:99-102, 1968

17. Meyer JS, Shimazu K, Okamoto S: Two separate mechanisms controlling cerebral blood flow: effect of alpha adrenergic blockage on cerebral autoregulation and chemical vasomotor control. Trans Am Neurol Assoc 98:284-286, 1973

18. Mchedlishvili G, Mitagvaria N: Vascular mechanisms controlling a constant blood supply to the brain. Stroke 4:742-750, 1973

19. Fieschi C, Agnoli A, Battistini N, et al: Derangement of regional cerebral blood flow and its regulatory mechanisms in acute cerebrovascular disease. Neurology 18:1166-1179, 1968

20. Kogure K, Scheinberg P, Fujiskima M: Effects of hypoxia on cerebral autoregulation. Am J Physiol 219:1393-1396, 1970

21. McDowall DG: Cerebral Circulation. Boston, Little, Brown and Company, 1969, p 564

Guest Discussion

EDWARD A. BRUNNER, MD, PhD
Department of Anesthesia
Northwestern University
Medical School
Chicago, Illinois

It may be worthwhile to consider the meaning of the term "autoregulation," as used in this paper. The authors describe it as "the ability of the brain to maintain an adequate flow consistent with its metabolic needs. . . ." Most physiologists would use a more restrictive definition which would relate flow, perfusion pressure, and vascular resistance. Metabolic considerations would be relegated to a possible mechanistic role.

The volume of flow (F) through an organ is pressure (P) dependent so long as the vascular resistance (R) in that organ is constant: $F = \frac{P}{R}$.

Under normal circumstances in the brain, however, the cerebrovascular resistance is not constant but is itself a function of perfusion pressure. Normally, as perfusion pressure increases, the cerebrovascular resistance also rises so that, although flow may increase, the increase is less than it would have been had resistance remained constant. Flow, then, tends to remain *relatively* constant despite alterations of perfusion pressure, within set limits. This is what is meant by the term "autoregulation." The reasons for these relationships of flow, pressure, and resistance are not yet clearly defined, but mechanisms based on both metabolic and myogenic factors have been postulated. Such considerations are beyond the scope of this discussion.

The "pressure" which functions in the autoregulation of CBF is the effective perfusion pressure, *not* the arterial pressure. The effective perfusion pressure in the brain differs from the arterial pressure by a value equal to the sum of the venous pressure plus the cerebrospinal fluid (CSF) pressure.

$$\text{Perfusion pressure} = \text{arterial pressure} - \left(\begin{matrix}\text{venous} \\ \text{pressure}\end{matrix} + \begin{matrix}\text{cerebrospinal} \\ \text{fluid pressure}\end{matrix}\right)$$

Note that I have not introduced the term "mean pressure" into the discussion at this point. The reason is that the role of pulsatile or nonpulsatile pressures has not yet been clearly defined in autoregulation of cerebral blood flow. Held and his coworkers[1] have shown that autoregulation is impaired by changing from pulsatile to

nonpulsatile perfusion pressure when a constant mean pressure is maintained, indicating that the character of the pressure curve as well as the absolute level of mean pressure is probably important in cerebral autoregulation.

In view of the factors cited above, studies purporting to investigate autoregulation or autoregulatory mechanisms should include measurements of venous pressure and CSF pressure in addition to the determination of arterial pressure, so that a determination of the perfusion pressure can be made. Additionally, some measure of the pulsatile character of the pressure wave should also be made in order to assess alterations in its character, to determine if this factor has an effect on measured alterations in the autoregulatory mechanism.

In applying these considerations to the study at hand, one would like to know whether measurements were made of venous pressure in the great veins draining the brain or of the CSF pressure. It would also be of interest to know if only the mean arterial pressure was recorded, as indicated in the figures, or whether the pulsatile character of the pressure wave was also recorded. These are important questions, since Ekström-Jodal's group[2] found that autoregulation did not occur in response to a reduction of perfusion pressure produced by alteration of venous pressure, but that it did occur when equivalent or greater reductions in perfusion pressure were produced by decreasing the arterial pressure.

Moreover, impairment of cerebral autoregulation has been produced by alteration from pulsatile to nonpulsatile perfusion pressure while maintaining mean pressure constant.[1] These factors must be fully considered before the importance of the findings reported in this study can be adequately evaluated. If, in fact, these factors have been adequately controlled in this study, the results will have great clinical implications to practicing anesthesiologists.

REFERENCES

1. Held K, Gottstein V, Niedermayer W: Cerebral blood flow in nonpulsatile perfusion, Cerebral Blood Flow. Edited by M Brock, C Fieschi, DH Ingvar, et al. New York, Berlin, Springer-Verlag, 1969, pp 94-96

2. Ekström-Jodal B, Haggendal E, Nilsson NJ, et al: Changes of the transmural pressure—the probable stimulus to cerebral blood flow autoregulation, Cerebral Blood Flow. Edited by M Brock, C Fieschi, DH Ingvar, et al. New York, Berlin, Springer-Verlag, 1969, pp 89-94

REPLY TO DR. BRUNNER'S COMMENTS

ANTHONY IVANKOVICH, MD

I thank Dr. Seldon for this opportunity to respond to Dr. Brunner's discussion, since time did not permit a reply after Dr. Miletich's oral presentation.

One could agree with Dr. Brunner's comments on the definition of "autoregulation;" however, after lengthy discussion, the authors chose a definition in accordance with that of Guyton:[1] "The term 'autoregulation' means regulation of blood flow through each local tissue in response to the tissue's own need for flow . . . to supply the tissue's needs for nutrients, no more, no less." My own preference for a definition is similar: "Autoregulation is the intrinsic tendency of an organ to maintain constant blood flow despite changes in arterial perfusion pressure."

I agree with Dr. Brunner's equation for "effective perfusion pressure." Theoretically, it is the pressure gradient forcing blood through cerebral vessels, being essentially the difference between mean arterial and mean venous pressures. However, I do not concur with Dr. Brunner's interpretation of the importance of the venous and CSF pressures in modifying the effective cerebral perfusion pressure. These pressures are comparatively small (0 to 6 torr and 10 to 20 torr, respectively); thus, for all practical purposes, perfusion pressure and MAP are essentially equivalent.

In several of our initial experiments, we measured the venous and CSF pressures and found that they increased only slightly during anesthesia. Following angiotensin or sodium nitroprusside injections, these pressures showed only minimal changes, compared with considerable changes in arterial pressure. In our experiments, changes in venous and CSF pressures had a negligible effect on perfusion pressures. Therefore, and since chronic catheterization of the jugular vein could lead to thrombosis and obstruction of cerebral venous outflow, we did not perform these measurements routinely.

There is ample experimental evidence that CBF is independent of perfusion pressure over the physiologic range (60 to 160 torr). Jacobson and coworkers[2] showed in dogs that when CVP was raised to 50 cm H_2O by constricting the superior vena cava, producing a reduction in effective perfusion pressures as low as 60 torr, there was no reduction in cerebral blood flow. In awake

man, Moyer and associates[3] demonstrated that when the jugular venous pressure was increased to 30 cm H_2O by inflating a cuff around the neck, causing a reduction in calculated perfusion pressure to 50 torr, there was no significant change in CBF.

The study by Ekström-Jodal's group,[4] cited by Dr. Brunner, is at variance with the above findings, since they reported a reduction in CBF when perfusion pressure was reduced by an increase in venous pressure (balloon in right atrium), but no change in CBF when perfusion pressure was reduced by arterial hypotension (bleeding). An important distinction in methodology between these studies is that the latter was performed with the brain surface exposed and covered by a plastic dome, perhaps requiring deep pentobarbital anesthesia, while extensive surgery may have resulted in cerebral trauma. In order to further amplify and clarify the lack of effect of changes in venous and CSF pressures on cerebral autoregulation, the reader is referred to two excellent monographs.[5,6]

As to Dr. Brunner's observations on the term "mean arterial pressure," and its implications in his reading of the pulsatile-nonpulsatile experiments of Held and coworkers,[7] MAP is widely used in the literature in reference to such measurements as cardiac output, peripheral vascular resistance, arterial pressure, right atrial pressure, etc, and there is a nearly universal use of "mean" arterial or perfusion pressure in correlation with changes in cerebral blood flow.[8]

The tracings in our figures show MAPs and mean flows derived by electronic integration of the phasic pressures and flows. The phasic flows are also shown on all tracings. Absence of the phasic arterial pressure on the tracings may have been misleading. It should be clear from our experimental design that the experiments were performed in the milieu of a physiologic pulsatile perfusion, as reflected by the phasic alterations in CBF shown in all the tracings. To further clarify this point a phasic arterial pressure tracing is shown here in the figure.

A careful reading of Held's paper reveals that even in the case of nonpulsatile perfusion, the ability to autoregulate is maintained, but at a higher flow level than pulsatile flow. These investigators concluded that ". . . cerebral autoregulation responds to both qualities of pressure: its pulsations and its constant component."

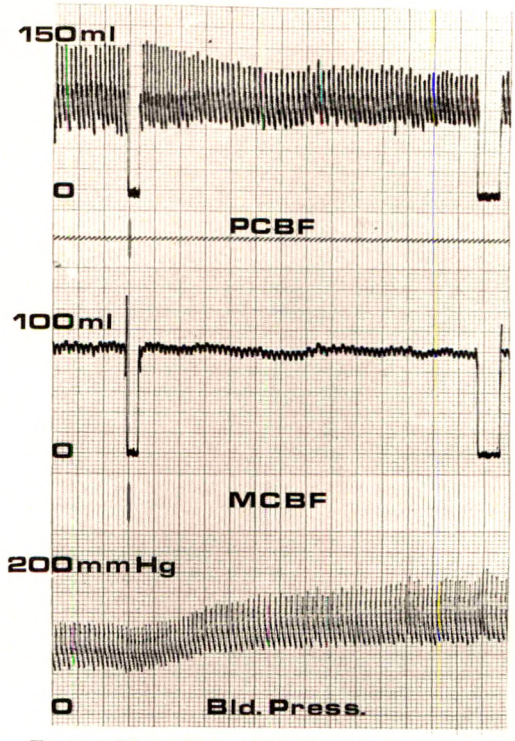


FIGURE. The effect of angiotensin infusion on phasic cerebral blood flow (PCBF), mean cerebral blood flow (MCBF) and phasic arterial blood pressure in the unanesthetized goat. Angiotensin produced an immediate increase in phasic arterial pressure, decreased the magnitude of phasic cerebral flow, but had no effect on mean cerebral flow.

I hope that I have adequately answered the questions raised by Dr. Brunner. We feel that our experiments represent a carefully controlled study which indicates that halothane and enflurane anesthesia do, in fact, impair cerebral autoregulation in the goat. Recently, Murphy, for Wollman and associates,[9] indicated that autoregulation of CBF in man appeared to be lost during anesthesia with halothane and enflurane. This supports our findings and further emphasizes their clinical significance.

REFERENCES

1. Guyton AC: Textbook of Medical Physiology. Philadelphia, WB Saunders Company, 1966 p 279

2. Jacobson I, Harper AM, McDowall DG: Relationship between venous pressure and cortical blood flow. Nature 200:173-175, 1963

3. Moyer JH, Miller SI, Snyder H: Effect of increased jugular pressure on cerebral hemodynamics. J Appl Physiol 7:245-247, 1954

4. Ekström-Jodal B, Haggendal E, Nilsson NJ, et al: Changes of the transmural pressure—the probable stimulus to cerebral blood flow autoregulation,

Cerebral Blood Flow. Edited by M Brock, C Fieschi, DH Ingvar, et al. New York, Berlin, Springer-Verlag, 1969

5. Harper AM: General physiology of cerebral circulation, Cerebral Circulation. Edited by DG McDowall. Boston, Little, Brown and Company, Int Anesthesiol Clin 7/3, 1969

6. Purves MJ: The Physiology of the Cerebral Circulation. Cambridge, Cambridge University Press, 1972

7. Held K, Gottstein V, Niedermayer W: Cerebral blood flow in non-pulsatile perfusion, Cerebral Blood Flow. Edited by M Brock, C Fieschi, DH Ingvar, et al. New York, Berlin, Springer-Verlag, 1969

8. Guyton AC, Jones CE, Coleman TG: Circulatory Physiology: Cardiac Output and Its Regulation. Philadelphia, WB Saunders Company, 1973

9. Murphy FL, Kennell EM, Johnstone RE, et al: The effects of enflurane, isoflurane, and halothane on cerebral blood flow and metabolism in man. Washington, DC, ASA Annual Meeting Abstracts, 1974, p 61

UMBILICAL ARTERY CATHETERIZATION Catheterization of the umbilical artery for monitoring critically ill neonates is standard practice. The authors report 15 major complications in 165 neonates related to an umbilical artery catheter. Arterial occlusion produced visceral infarction in 12 patients and vascular perforation caused hemoperitoneum in 3 patients. The duration of catheterization in these 15 neonates was 3 times that in the other 150 infants. The potential for visceral infarction increased as the catheter tip was placed more cephalad in the aorta. Roentgenographic confirmation of catheter tip location below the kidneys, avoidance of catheter manipulation and removal when no longer needed should reduce the incidence of iatrogenic complications. *(Marsh JL, King W, Barrett C et al: Serious complications after umbilical artery catheterization for neonatal monitoring. Arch Surg 110:1203-1208, 1975)*

Successful Use of a Reduced Dose of Protamine After Cardiopulmonary Bypass

ANITA V. GUFFIN, MMS*
RONALD W. DUNBAR, MD†
JOEL A. KAPLAN, MD‡
JAMES W. BLAND, JR., MD§
Atlanta, Georgia‖

The dose of protamine necessary to reverse heparin was examined in 60 patients. Half the patients (controls) received a reversal dose of protamine equal to the entire amount of heparin given them, while half received a reversal dose based on a heparin half-life of 2 hours. Postoperative chest drainage for the first 12 hours and for 48 hours was markedly reduced in patients given the reduced dose of protamine. Platelet counts were higher and postoperative clotting studies varied less from control in patients receiving the smaller dose of protamine. The authors suggest reevaluation of the dose of protamine necessary to reverse the anticoagulant effects of heparin in patients for cardiopulmonary bypass, since larger doses of protamine may contribute to the conditions which increase postoperative bleeding.

A MAJOR problem following cardiopulmonary bypass is reversal of the anticoagulant. Heparin is recognized as the most effective anticoagulant, and protamine sulfate, originally recognized as an anticoagulant itself, is now generally used to reverse the anticoagulant action of heparin.[1-3]

Whether excess protamine actually contributes to postoperative bleeding is still controversial.[4-6] In general, dosage is 1 to 4 mg of protamine sulfate per milligram of heparin administered during the procedure. Our study investigated the use of a reduced dose of protamine, to determine its effect on postoperative bleeding and clotting.

METHODS

Two groups of 30 patients undergoing coronary artery bypass procedures were studied (table 1). All patients were anesthetized with morphine sulfate (0.3 to 0.5 mg/kg), diazepam (0.2 to 0.3 mg/kg), and N_2O-O_2, with either pancuronium bromide or d-tubocurarine for relaxation. All had two intravenous infusions. Central venous and direct arterial pressure, ECG, and esophageal and rectal temperatures were monitored, and arterial blood gases were measured throughout the procedure by a Radiometer Copenhagen Model BMS3 Blood Gas Analyzer. Serum potassium was measured every

*Anesthesia Assistant.

†Professor of Anesthesiology.

‡Assistant Professor of Anesthesiology.

§Associate Professor of Anesthesiology and Pediatrics.

‖Division of Cardiothoracic Anesthesia, Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia 30322.

Reprint requests: Ronald W. Dunbar, M.D., Department of Anesthesiology, Emory University Hospital, Atlanta, Georgia 30322.

Paper received: 4/21/75
Accepted for publication: 6/11/75

TABLE 1
Patients Studied

Group	Number	Age Mean ± SE	Weight, kg Mean ± SE
A (controls)	30	46.1 ± 2.6	69.6 ± 2.5
B (experimental group)	30	47.5 ± 2.4	67.0 ± 2.6

No significant differences.

30 minutes during the procedure and potassium chloride was administered to maintain a level of approximately 4.5 mEq/L.

Beef lung heparin (3 mg/kg) was administered initially, and 1.5 mg/kg was given at 2-hour intervals during bypass. Body temperature was reduced to 28 to 30° C for the greater portion of the bypass period. A Bentley-Temptrol oxygenator was used for all patients. The priming volume of the pump consisted of 1500 ml of Normosol®, 500 ml of dextran, 22.5 gm of mannitol, and 500 ml of whole blood. Following bypass, each patient received an average of 3 units of whole blood. In group A, 6 patients received 2 units of fresh-frozen plasma and 12 patients received 5 units of platelets. In group B, 7 patients received 2 units of fresh-frozen plasma and 4 patients received 6 units of platelets. All blood products were administered following collection of blood samples for coagulation studies.

Following bypass, group A was given a reversal dose of protamine that was a milligram-for-milligram equivalent of the entire amount of heparin given during the procedure. Group B was given a reduced dose of protamine based on a heparin half-life of 2 hours. Calculations were based on a straight-line decay that assumed 75 percent of the original heparin remained after 1 hour and 50 percent remained after 2 hours. We administered heparin in half the original dose after 2 hours and assumed this would bring the patient again to full heparinization.

For example, a patient given 200 mg of heparin at 1000 hr would receive another 100 mg for reheparinization at 1200 hr. At 1300 hr, a patient in group B would receive 150 mg of protamine to reverse the residual heparin. This assumes 75 percent of the original dose would require reversal. In contrast, a patient in group A would receive 300 mg of protamine.

Protamine was administered over 10 to 15 minutes, and clotting studies were drawn 10 minutes after the patient had received the total dose of protamine. Chest drainage was measured for the first 12 hours postoperatively and for the total indwelling of the chest tubes (approximately 48 hours). Coagulation parameters studied were prothrombin time, partial thromboplastin time, and platelet count. All statistical comparisons were made by Student's *t*-test.

RESULTS

The control group (A) received significantly more heparin than the experimental group (B), due to the slightly greater weight of the patients. Group B received less protamine than group A; this difference was highly significant ($p<0.005$) (table 2).

Group B patients showed significantly less variation of prothrombin time and partial thromboplastin time (table 3). These differences were both significant ($p<0.005$). The platelet count averaged 40,000 higher

TABLE 2
Heparin and Protamine Dosage

Group	Heparin, mg Initial Mean ± SE	Heparin, mg Total Mean ± SE	Protamine, mg Mean ± SE
A	213.7 ± 84.0	290.0 ± 16.1	333.7 ± 20.4
B	202.2 ± 77.1	229.2 ± 11.4*	105.2 ± 4.1†

*$p < 0.01$ by Student's *t*-test compared with group A.

†$p < 0.005$ by Student's *t*-test compared with group A.

TABLE 3
Coagulation Parameters

	Group A Mean ± SE	Group B Mean ± SE	Significance*
Prothrombin time (sec > control)	4.42 ± 0.36	2.96 ± 0.19	$p < 0.005$
Partial thromboplastin time (sec > control)	6.15 ± 1.23	0.57 ± 0.75	$p < 0.005$
Platelet count after bypass	85,013 ± 6837	124,067 ± 5779	$p < 0.005$

*Student's *t*-test comparing groups A and B.

TABLE 4
Postoperative Chest-Tube Drainage

Group	1st 12 hours Mean ± SE	48 hours Mean ± SE
A	702 ± 84.5	1136 ± 135.4
B	363 ± 28.8*	623 ± 40.5*

*$p < 0.005$ by Student's t-test compared to group A.

in group B ($p<0.005$), in which group the lowest platelet count postoperatively was 79,000. Eight patients in group A had platelet counts of less than 60,000, and 1 patient had a platelet count of 6400 after bypass. Platelet function was not studied.

Postoperative chest drainage of blood was also significantly less in the experimental group with a reduced dose of protamine (table 4).

Cardiopulmonary bypass time was about the same for both groups (table 5), but time after bypass was considerably shorter in group B ($p<0.005$), probably because of less bleeding and oozing, permitting quicker closure of the chest. Total surgical time was also 1 hour less in group B ($p<0.005$).

DISCUSSION

Various reports show protamine dosage for heparin reversal to range from none[7] to 4 times the amount of heparin given during the operation.[2,4,5] Frequently, the reversal dose of protamine equals the total amount of heparin given.[4,5]

Heparin is repeated in doses equal to one-half of the original dose at time intervals of 1 to 2 hours, depending on the dose schedule used by different authors.[4,8,9] This rationale is based on studies showing the half-life of heparin to be dependent on temperature and dosage, and to increase with larger doses.[9,10] Therefore, unless heparin has just been administered, it is recognized that some of the heparin has been catabolized, bound, or excreted, leaving only a portion of the original amount to be reversed.

Though the half-life decay of heparin is uneven, we used a straight-line approximation based on a half-life of 2 hours. The half-life of 1, 2, and 4 mg/kg injected IV is 56, 96, and 152 minutes, respectively.[10] Previous studies have shown a half-life of 3 mg/kg to be 1.75 hours at 37 C and 2.5 hours at an average temperature of 22 to 23 C.[9] Since all our patients were exposed to a period of decreased temperature of 28 to 30 C during the procedure, the half-life of heparin (3 mg/kg) was estimated to be 2 hours.

The dose of 1 mg of protamine for each milligram of heparin administered to our controls was based on studies showing that protamine is not a significant anticoagulant in moderate overdosage, and that this dose was in a safe range.[4] In fact, Ellison's studies[4] suggest that overdosage of protamine might be given to ensure complete reversal of heparin without threat of the anticoagulant effects of protamine. However, this amount was 2 to 5 times greater than the calculated dose would have been using a heparin half-life of 2 hours. Other reports indicate only minimal protamine inhibition of clotting.[1,2,6,8] Comparing the dose of protamine given to our controls with the dose that would have been administered according to the protocol for the experimental group, the excess protamine administered averaged 203 mg per patient.

Though heparin rebound has been pointed out as a possible threat with small doses of protamine,[11] our study seems to indicate that the rebound may be only a laboratory value, and that it does not significantly increase postoperative bleeding. This is shown by the 50% reduction in 12-hour chest drainage and the 45% reduction in 48-hour chest drainage for group B.

Some evidence[8] indicates that protamine can cause platelet agglutination and disappearance of platelets; this may explain why platelet count was greater by approximately 40,000 in the group with the reduced

TABLE 5
Surgical Times (Minutes)

Interval	Group A Mean ± SE	Group B Mean ± SE	Significance*
Cardiopulmonary bypass	135.5 ± 14.8	121.1 ± 10.3	NS
After bypass	134.6 ± 7.1	96.5 ± 4.2	$p < 0.005$
Total surgical time	358.7 ± 19.4	293.0 ± 14.5	$p < 0.005$

*Student's t-test comparing groups A and B.

protamine dosage. Thrombocytopenia sometimes follows cardiopulmonary bypass; administration of excess protamine may aggravate this condition. However, no laboratory verification of this has been documented.

In summary, we believe the dose of protamine used to reverse heparin during cardiac surgery needs reassessment. Smaller doses led to decreased postoperative bleeding in our study, and there was no clinically apparent heparin rebound. We believe heparin activity and protamine reversal should be more closely monitored intraoperatively by frequent coagulation tests. Studies along this line are currently in progress.

REFERENCES

1. Hurt R, Perkins HA, Osborn JJ, et al: The neutralization of heparin by protamine in extracorporeal circulation. J Thorac Surg 32:612-619, 1956

2. Hawksley M: De-heparinisation of blood after cardiopulmonary bypass. Lancet 1:563-565, 1966

3. Chargaff E, Olson KB: Studies on the chemistry of blood coagulation. VI. Studies on the action of heparin and other anticoagulants. The influence of protamine on the anticoagulant effect in vivo. J Biol Chem 122:153-167, 1937-38

4. Ellison N, Ominsky AJ, Wollman H: Is protamine a clinically important anticoagulant? Anesthesiology 35:621-629, 1971

5. Rothnie NG, Kinmonth JB: Bleeding after perfusion for open heart surgery. Importance of unneutralized heparin and its proper correction. Brit Med J 1:73-78, 1960

6. Anderson MN, Mendelow M, Alfano GA: Experimental studies of heparin-protamine activity with special reference to protamine inhibition of clotting. Surgery 46:1060-1068, 1959

7. Castaneda AR: Must heparin be neutralized following open-heart operations? J Thorac Cardiovasc Surg 52: 716-724, 1966

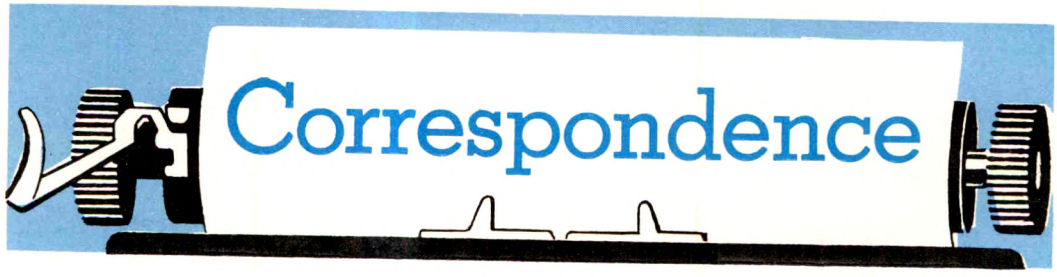
8. Jaques LB: Protamine—antagonist to heparin. Canad Med Assoc J 108:1291-1297, 1973

9. Wright JS, Osborn JJ, Perkins HA, et al: Heparin levels during and after hypothermic perfusion. J Cardiovasc Surg 5:244-250, 1964

10. Goodman LS, Gilman A: The Pharmacological Basis of Therapeutics. New York, The Macmillan Company, 1970, p 1449

11. Ellison N, Beatty P, Blake DR, et al: Heparin rebound. J Thorac Cardiovasc Surg 67:723-729, 1974

THE INFLUENCE OF THE ROUTE OF ADMINISTRATION ON THE CLINICAL ACTION OF DIAZEPAM. In a "double-blind, double-dummy" study in 200 adult women, closely matched as to age, weight, and physical fitness, diazepam by mouth, buttock, and/or thigh (IM) was investigated for comparison of efficacy, side effects, and especially pain of injection. The systemic analgesic effect of combining oral and IM diazepam was not notably greater than that of the single oral dose. As the injection of diazepam was followed by an unacceptably high incidence of pain, the oral administration of this drug should be the route of choice. *(Assaf, Dundee, Gamble. Anaesthesia 30:152-158, 1975.)*



To the Editor:

I feel compelled to comment on the recent article by Howland and associates, "Fibrinogen and albumin deficiencies associated with packed red blood cell transfusions, (Anesth & Analg 54:89-93, 1975) which contains errors and misconceptions that must not go unchallenged. The authors describe a liver-transplant patient who received 35 units of packed red blood cells resuspended in normal saline solution during the course of a 14-hour operation. They state that "packed cells were selected in preference to whole blood in an effort to avoid white-cell interference with immunologic mechanisms." If by this somewhat ambiguous statement they mean to imply that the white blood cell content of packed red blood cells, as the term is commonly used, differs in any way from that of whole blood, they are mistaken. Of blood products commonly available, only frozen red blood cells or leukocyte-poor (buffy-poor) red blood cells have most of the white blood cells removed. Although not stated in the article, I assume that the reason the authors chose not to administer platelet concentrates to their patient (a product clearly indicated in large quantities for any patient receiving 35 units of blood during a 14-hour surgical procedure) was their reluctance to expose their patient to the transplant antigens which platelets are known to carry as well as to the white blood cells inevitably present in platelet concentrates.

Although lamenting the absence of fibrinogen in purified protein fraction, they fail to mention the use of single-donor plasma as a suitable product for volume expansion. Single-donor plasma contains normal levels of fibrinogen as well as all other plasma

proteins. Their reluctance to administer single-donor plasma may be related to the minimal hepatitis risk of the product, a risk not present with albumin or purified protein fraction. Their patient had a substantial intraoperative exposure to blood, and judicious use of single-donor plasma, in my opinion, would have been warranted, particularly when the hepatitis risk is weighed against the clinical consequences of the greatly depressed fibrinogen level their patient displayed postoperatively.

I can find no fault with the authors' conclusion that if you remove the plasma from a unit of whole blood and replace it with normal saline, the total protein and fibrinogen in the unit will decline.

Bruce A. Friedman, MD
Associate Director, Blood Bank
University Hospital
University of Michigan
Ann Arbor, Michigan

* * *

To the Editor:

In reply to Dr. Friedman's letter concerning the article "Fibrinogen and albumin deficiencies associated with packed red blood cell transfusions," we inadvertently omitted to say that the packed cells in the case under discussion were white-cell poor.

Apropos of the necessity for administering platelets during massive blood replacement, we differ from Dr. Friedman. Although bank blood is deficient in platelets and the platelet count does fall in these patients, we have been able to control bleeding very effectively without the use of platelets. Platelets are employed only in those cases in which the thromboelastograph indicates poor platelet function. The latter cases are very few.

William S. Howland, MD
Department of Anesthesia
Memorial-Sloan-Kettering Cancer Center
New York, New York

To the Editor:

I wish to comment on the excellent paper, "Plasma Concentration of Lidocaine after Endotracheal Spray," by Chu and associates (Anesth & Analg 54:438-441, 1975).

In 1972, at the Fifth World Congress of Anaesthesiologists, we[1] reported on a similar investigation measuring the uptake of lidocaine from the trachea. A summary of the work follows:

Thirty patients admitted for minor nose and throat surgery were premedicated similarly with hydroxyzine, 50 mg; pentobarbital, 1.5 mg/kg; and atropine, 0.4 to 0.8 mg IM, 1 hour before operation. Anesthesia was induced with thiopental, 5 mg/kg, and tracheal intubation facilitated with succinylcholine, 1.5 mg/kg. Lidocaine in concentrations of 2 or 4% was instilled via a Steiner cannula into the trachea at a dose of 2 mg/kg prior to intubation. Anesthesia was maintained throughout the procedure with N_2O-O_2 (50-50) and 1 to 2% halothane. During this project, no toxic effects of lidocaine were recorded.

Venous blood samples were collected at 0, 5, 10, 20, 30, 60, 90, and 120 minutes. The blood samples were centrifuged and the serum extracted for lidocaine and its metabolites by the method of Edhorn.[2]

Analyses were with a series-104 gas-liquid chromatograph (WG Pye), equipped with dual flame ionization detector and a Philips PM 8000 recorder. The injection part and detector were maintained at 280 C and the oven at 170 C for the first 5 minutes after injection and then programmed at 12 C/min to 240 C. A Pyrex-glass coiled column, 1.5 m long with 0.635 cm OD, packed with Chromsorb(R), was used for analyses. Gas flow rates were H_2, 50 ml/min; air, 600 ml/min; and N_2, 40 ml/min.

A significant and continual rise of lidocaine and its metabolites in plasma resulted throughout the first 30 to 60 minutes, followed by a gradual decline in plasma levels thereafter. Similar results were obtained with 2 and 4% lidocaine.

The plasma level of lidocaine rarely exceeded 1 μg/ml. Glycine xylidide was by far the major metabolite seen in the plasma, with blood levels frequently exceeding 8 μg/ml. Monoethyl glycine xylidide plasma levels were below those of lidocaine and only occasionally was the parahydroxy metabolite observed at the lower limits of detection (0.2 μg/ml). The peak blood levels of lidocaine in the 30 patients ranged from a low of 0.1 μg/ml to a high of 2.0 μg/ml.

It appears that the work of Chu's group confirms our finding that the uptake of lidocaine from the upper trachea under the conditions described is slower than when given IV.

In 1965, Telivuo[3] also found a slow absorption of lidocaine from the respiratory tract with spontaneous ventilation.

R. Brian Smith, MD
Department of Anesthesiology
University Health Center of
Pittsburgh
Pittsburgh, Pennsylvania

REFERENCES

1. Cohn ML, Smith RB, Sievenpiper T: Concentrations of lidocaine and its metabolites in the blood after endotracheal administration. Fifth World Congress of Anaesthesiologists. Excerpta Medica 261:118-119, 1972

2. Edhorn GA: Determination of lidocaine in whole blood by gas chromatography. Can Anaesth Soc J 18:189-198, 1971

3. Telivuo L: An experimental study on the absorption of some local anaesthetics through the lower respiratory tract. Acta Anaesthesiol Scand Suppl 16:121-133, 1965

* * *

To the Editor:

Thank you for sending me a copy of Dr. Smith's letter. Dr. Smith and I both agree that the rate of absorption of local anesthetic administered through endotracheal spray in supine anesthetized patients shows significant delay as compared with the IV route.[1,2] The differences between the lidocaine blood concentration in Dr. Smith's group of patients and ours may be due to dosage (2 mg/kg versus mean 3.3 mg/kg body weight), and the cannula used (Steiner versus LTA).

The metabolic pathway of lidocaine was well illustrated by DiFazio and Brown.[3] The major metabolite of lidocaine was found to be monoethylglycinexylidide (MEGX),[3,5] 20 to 76% of the lidocaine level. The level of glycinexylide (GX) was lower, 12 to 16% of the lidocaine concentration. Both MEGX and GX are pharmacologically active and may contribute to the CNS stimulation by lidocaine.[4,6] On a weight basis, MEGX has 88% and GX 54% the antiarrhythmic potency of lidocaine, and GX was 27% as potent as MEGX. In man, 41 to 58% of the administered GX was excreted unchanged by kidneys, 4.3 to 4.8% underwent metabolic transformation and appeared in urine as conjugates of xylidine and p-OH xylidine, and the fate of the rest was unknown.

The results obtained by Dr. Smith's group showed that GX was by far the major metabolite and its plasma concentration often exceeded that of lidocaine. This is an interesting finding. More studies are needed to understand the difference in the

pharmacokinetics between IV and endotracheal routes of lidocaine administration.

I appreciate very much Dr. Smith's comments.

Stephen S. Chu, MD
Department of Anesthesiology
Medical College of Virginia
Virginia Commonwealth University
Richmond, Virginia

REFERENCES

1. Chu SS, Rah KH, Brannan MD, et al: Plasma concentration of lidocaine after endotracheal spray. Anesth & Analg 54:438-441, 1975

2. Cohn ML, Smith RB, Sievenpiper T: Concentration of lidocaine and its metabolites in the blood after endotracheal administration. Fifth World Congress of Anaesthesiologists. Excerpta Medica 261:118-119, 1972

3. DiFazio CA, Brown RE: Lidocaine metabolism in normal and phenobarbital-pretreated dogs. Anesthesiology 36:238-243, 1972

4. Collinsworth KA, Strong JM, Atkinson AJ Jr, et al: Pharmacokinetics and metabolism of lidocaine in patients with renal failure. Clin Pharmacol Ther 18:59-64, 1975

5. Strong JM, Mayfield DE, Atkinson AJ Jr, et al: Pharmacological activity, metabolism and pharmacokinetics of glycinexylidide. Clin Pharmacol Ther 17:184-194, 1975

6. Halkin H, Meffin P, Melmon KL, et al: Influence of congestive heart failure on blood levels of lidocaine and its active monodiethylated metabolites. Clin Pharmacol Ther 17:669-679, 1975

* * *

To the Editor:

In the May-June 1975 issue, Forestner and Raj[1] report on the inadvertent injection of a 2% solution of thiopental into the epidural space. They were successful in handling the problem and the patient was not harmed. My comment concerns a statement made in the discussion of the problem. The authors say, "The lower pH (4.1) of the local anesthetic mixture would also retard thiopental absorption." I would like to ask the authors about the mechanism of this pH effect.

Offhand, I would have assumed it would work the other way around. Since thiopental is a weak acid with a pK of 7.6, any acidification of the thiopental solution should increase the unionized fraction of the thiopental while decreasing the ionized fraction. This would mean that, with falling pH, the amount of unionized, ie, absorbable and diffusible, thiopental would increase as pH falls. This mechanism should, if my assumptions are correct, be particularly useful if the pH could be lowered in the compartment that contains the thiopental but not in the compartment which is to receive the thiopental.

I am also assuming that pH would not actually fall to 4.1 but would change in a range in which a shift from ionized to unionized would still be of clinical significance.

J. S. Gravenstein, MD
Department of Anesthesiology
University Hospitals
Cleveland, Ohio

REFERENCE

1. Forestner JE, Raj PP: Inadvertent epidural injection of thiopental: a case report. Anesth & Analg 54:406-407, 1975

* * *

To the Editor:

In considering Dr. Gravenstein's question, we have found it necessary to distinguish between blood solubility and membrane diffusibility of thiopental. At physiologic pH in blood, thiopental solubility is limited to 1.2 mg/ml. To increase solubility, the pH is raised to 10.6 with sodium carbonate, to permit concentrations of 20 mg/ml and higher. Decreasing the pH of thiopental solutions after injection into the bloodstream can be shown to favor precipitation, and crystals can be filtered from blood collected proximally.[1] Thus, we sought to hinder absorption of the thiobarbiturate by lowering its pH with local anesthetic solution, causing precipitation of acid thiopental. In vitro, an equal mixture of 2% thiopental and bupivacaine-lidocaine, as described in our case report, would achieve a pH of 8.8, with visible precipitation of thiobarbiturate.

Dr. Gravenstein suggests that the diffusion of thiopental across membranes would be facilitated by acidification, rather than impeded. We would have to agree that absorption of thiopental would be better at lower pH, with progressive increases in the unionized fraction. It was our thought that less thiopental would be available for absorption after precipitation of the drug. Perhaps a better choice of wording would have been "to promote thiopental precipitation." Whether this precipitation would significantly retard the rise of serum thiopental concentrations, given the increased absorption to be expected, would remain to be determined. We appreciate Dr. Gravenstein's correction.

John E. Forestner, MD
P.P. Raj, MD
Department of Anesthesiology
University of Texas
Southwestern Medical School
Dallas, Texas

REFERENCE

1. Waters DJ: Intra-arterial thiopentone. Anaesthesia 21:346-356, 1966

To the Editor:

In your issue for May-June 1975, there was yet another article on awake intubation,[1] the authors inflicting this trauma on no less than 37% of their patients, noting en passant that anesthetists pay only lip service to this technic.

As one who does less than pay lip service to this technic, I would like through your columns to explain why. As a resident, I spent considerable time reading, from the experts, the pros and cons of the head-up, the head-down, and the flat positions, with or without cricoid pressure, with or without topical analgesia, etc. The recommendations are often dogmatic and often conflicting.

In the interests of simplicity, I opted for the Trendelenburg position, and since that decision, in 8 years of anesthesia practice, I have never had an aspiration, despite numerous inductions--both intravenous and gaseous--of patients with full stomachs, intestinal obstruction, and so on. With the patient induced in Trendelenburg, I have on many occasions seen copious amounts of fluid run harmlessly onto the floor and simultaneously inserted an endotracheal tube into a trachea as dry as a bone. The procedure is simple and requires no special equipment and is always available. The alternatives, as described numerous times previously, are meddlesome and traumatic both emotionally and physically for the patient, and do not provide a better standard of care.

Kenneth W. Green, MD
Department of Anesthesia
Thayer Hospital
Waterville, Maine

REFERENCE

1. Kopman AF, Wollman SB, Ross K, et al: Awake endotracheal intubation: a review of 267 cases. Anesth & Analg 54:323-327, 1975

* * *

To the Editor:

I have been following closely the "debate" on intermittent mandatory ventilation that has appeared in your Journal. There apparently is a side to this issue which could use some emphasis at this time. Successful weaning from mechanical ventilation requires careful monitoring for ultimate patient safety, with multiple T-tube trials. In a small community hospital such as I practice in, this may severely stress the available resources. IMV facilitates safe patient management in a number of ways:

1. Handling of the intubated airway is reduced, since weaning time is advanced by changing the machine settings and not by switching from machine to T-tube. This also means that if a patient tires at one setting, the machine setting can be altered simply and the patient safely returned to a different ventilatory level without risking accidental disconnection or contamination of the airway or trauma produced by manipulation of the tube.

2. Since spontaneous ventilation may persist, the patient is allowed to control his own Pa_{CO2} to some extent, thus avoiding easy passive hyperventilation to profound levels of alkalosis with associated CSF acid-base changes that may retard or complicate eventual independence from the ventilator. This is most important in patients with chronic lung disease.

3. Other problems such as "ventilatory-discoordination," accidental disconnection, and extreme requirements for sedation and/or paralysis are managed more effectively with IMV. Patients appear to be far more consistently in coordination with the machine at all settings than with other patterns of mechanical ventilation.

Most of our patients are elderly, with siginificant chronic lung disease. The almost universal use of IMV has made mechanical ventilation more efficient, easier to manage, safer, and has markedly increased ICU-personnel morale.

Kenneth M. Janis, MD
Saddleback Community Hospital
Laguna Hills, California

ANTIEMETIC EFFECT OF THC Oral delta-9-tetrahydrocannabinol (THC) was compared with a placebo as an antiemetic for nausea and vomiting following cancer chemotherapeutic drugs. Oral THC (10 mg/m^2) was an effective antiemetic in 14 of 20 courses while the placebo was ineffective in all instances. The lack of THC effect in some patients may be related to failure of gastrointestinal absorption. No patient vomited while experiencing a "high" from THC. Although somnolence often occurred with this THC dose, a significant curtailment of activities was infrequent. Toxicity (fear, panic, hallucinations) occurred in only two patients, both after three THC doses of 20 mg. *(Sallan SE, Zinberg NE, Frei E: Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. NEJM 293:795-797, 1975)*

Effect of Mechanical Ventilation with End-Inspiratory Pause on Blood-Gas Exchange

SAMIR F. FULEIHAN, MD*
ROGER S. WILSON, MD†
HENNING PONTOPPIDAN, MD‡
Boston, Massachusetts§

The effects of end-inspiratory pause (EIP) on gas exchange were measured in 10 adult patients with acute respiratory insufficiency while maintained on mechanical ventilation. Four inspiratory patterns were studied with a constant tidal volume (10 to 15 ml/kg body weight), respiratory rate (9 to 12 breaths/min), F_{IO_2} (0.5) and end-expiratory pressure. Inspiratory flow rate ($\dot{V}_{insp}$) and EIP time were varied to produce a control pattern ($\dot{V}_{insp}$ = 60 L/min, EIP = 0), 2 EIP patterns of 0.6 and 1.2 seconds with a similar $\dot{V}_{insp}$ and a "slow" flow pattern ($\dot{V}_{insp}$ = 30 L/min) without EIP. The control pattern was applied before and after each study period.

Arterial oxygenation was unchanged with both EIP and "slow" flow patterns when compared to control. Dead-space ventilation (V_D/V_T) and P_{aCO_2} were significantly decreased ($p<0.01$) as EIP was increased from 0 to 1.2 seconds, but remained unchanged with slow inspiratory flow. Thus, EIP improved the efficiency of ventilation with no apparent improvement in oxygenation in patients with acute respiratory insufficiency.

FLOW and pressure patterns produced by various ventilators differ widely and have varying effects on the efficiency of gas exchange. End-inspiratory pause (EIP) is a ventilatory pattern characterized by a period of no-flow occurring at the end of inspiration. The inspired tidal volume is retained in the lungs for a finite period of time, resulting in a prolongation of "inspiration" without airway gas flow.[1]

Previous studies using lung models have shown that uneven distribution of ventilation resulting from regional differences in airway resistances may be improved by the addition of a no-flow interval at the end of inspiration.[2-4] In addition, studies in anesthetized animals have demonstrated an improved alveolar ventilation ($\dot{V}_A$) and ventilation to perfusion ratio ($\dot{V}_A/\dot{Q}$) when EIP is included in the pattern of ventilation.[5,6] The purpose of this study was to determine whether addition of EIP to a ventilatory pattern has any beneficial effect on blood-gas exchange in patients with acute respiratory insufficiency (ARI).

*Instructor in Anesthesia.

†Assistant Professor of Anesthesia.

‡Professor of Anesthesia.

§Respiratory Intensive Care Unit and Anesthesia Laboratories of the Harvard Medical School at the Massachusetts General Hospital, Boston, Massachusetts 02114.

Read at the 49th Congress of the International Anesthesia Research Society, March 16-20, 1975, Hollywood, Florida.

This study was supported in part by Grant GM-15904-08 from the National Institute of General Medical Sciences.

Reprint requests to: Dr. Wilson.

Paper received: 7/21/75
Accepted for publication: 9/15/75

METHODS

Ten adult patients with ARI of varying etiology were studied at a time of stable respiratory and cardiovascular function. Salient anthropometric and medical details are summarized in tables 1 and 2.

All patients were studied in the semisitting position. Each had a cuffed endotracheal or tracheostomy tube with an airtight fit. Patients were ventilated mechanically and were well in phase with the ventilator cycling. One hour prior to the study, they were switched from the ventilator used clinically to a volume-preset, constant-flow generator* which incorporated a variable inspiratory hold time (0.2 to 2 sec.).

*Gill I, Chemetron Medical Products, St. Louis, Missouri.

TABLE 1
Patients Studied—Clinical Data

Patient	Sex	Age	Diagnosis	Chest x-ray
1	M	45	Multiple fractures (ribs, hip, pelvis)	LLL atelectasis
2	F	87	Multiple rib fractures; S/P respiratory arrest	Clear
3	F	66	Guillain-Barré	LLL infiltrate
4	M	64	COPD, kyphoscoliosis, S/P transthoracic wiring of aortic aneurysm	Left pleural effusion
5	M	54	Systemic lupus erythematosus with "Guillain-Barré"	Clear
6	F	73	Multiple fractures (pelvis, femur), renal failure	Diffuse pulmonary edema, left pleural effusion
7	F	59	Guillain-Barré with tracheo-esophageal fistula	Resolving LLL atelectasis
8	F	65	Peritonitis, flail chest, hepatic and renal failure	Diffuse interstitial pulmonary congestion
9	M	64	Intracerebral hematomas (evacuated), old myocardial infarction, congestive heart failure	Diffuse pulmonary edema
10	F	79	Respiratory arrest following abdominal surgery	LLL pneumonia, left pleural effusion

LLL = left lower lobe.
S/P = status post.
COPD = chronic obstructive pulmonary disease.

TABLE 2
Patients Studied—Respiratory Status

Patient	F_{IO_2}	PEEP, cm H_2O	$AaDO_2^{1.0}$	Plateau compliance*	FRC, ml	FRC, % of normal
1	0.40	0	352	45	946	25
2	0.30	0	185	38	1530	70
3	0.40	+5	390	59	2300	79
4	0.40	0	305	77	—	—
5	0.25	0	137	37	2680	90
6	0.50	+12	339	37	1150	39
7	0.35	0	234	43	—	—
8	0.30	+6	306	29	—	—
9	0.50	+4	283	79	—	—
10	0.45	0	372	38	—	—

*Plateau compliance: described in text.

Four ventilatory patterns were studied while all the following were maintained constant: *tidal volume* (V_T = 10 to 15 ml/kg body weight), *respiratory rate* (9 to 12 breaths/min), *inspired O_2 concentration* (F_{IO_2} = 0.5) and *end-expiratory pressure* (EEP). In 4 patients (#3, 6, 8, 9), where positive end-expiratory pressure (PEEP) was used in clinical management, it was maintained at the same level during the study. *Inspiratory flow rate* ($\dot{V}_{insp}$) and *EIP time* were varied to produce a control pattern ($\dot{V}_{insp}$ = 60 L/min, EIP = 0), 2 EIP patterns of 0.6 and 1.2 seconds ($EIP_{0.6}$ and $EIP_{1.2}$) with a similar $\dot{V}_{insp}$ and a "slow" flow pattern ($\dot{V}_{insp}$ = 30 L/min) without EIP (table 3). The control pattern was interspaced before and after each study period. Each pattern was maintained for a period of 45 to 60 minutes, during which the following hemodynamic and ventilatory measurements were made:

Vital Signs.—Heart rate and rhythm were recorded continuously; blood pressure and central venous pressure (CVP) were determined at 5-minute intervals, and urine output was measured hourly.

$AaDO_2^{0.5}$: alveolar-arterial oxygen difference measured at F_{IO_2} = 0.5.
ARI: acute respiratory insufficiency.
C_T: total compliance.
CVP: central venous pressure.
EEP: end-expiratory pressure.
EIP: end-inspiratory pause.
EIPP: end-inspiratory plateau pressure.
F_{ECO_2}: mixed expired CO_2 concentration.
F_{IO_2}: inspired O_2 concentration.
FRC: functional residual capacity.
I/E: inspiratory:expiratory ratio.
IP: Inspiratory pressure.
MAP: mean airway pressure.
P_B: atmospheric pressure.
P_{ECO_2}: mixed expired CO_2 tension.
PEEP: positive end-expiratory pressure.
$P_{H_2O}T$: water vapor pressure at body temperature (T).
PIP: peak inspiratory pressure.
Q_S/Q_T: intrapulmonary right-to-left shunt (expressed as percentage of cardiac output).
RR: respiratory rate.
$\dot{V}_A$: alveolar ventilation.
$\dot{V}_A/\dot{Q}$: ventilation:perfusion ratio.
$\dot{V}CO_2$: carbon dioxide production.
V_{comp}: compressible volume.
$V_D$app: dead-space volume of mechanical apparatus.
V_Dm: measured dead-space volume.
$V_D$phys: physiologic dead-space volume.
V_D/V_T: dead-space:tidal-volume ratio.
$\dot{V}_{insp}$: inspiratory flow rate.
V_T: tidal volume.

TABLE 3
Specific Ventilatory Patterns Evaluated

Ventilatory pattern	$\dot{V}_{insp}$, L/min	EIP, sec
Control	60	0
$EIP_{0.6}$	60	0.6
$EIP_{1.2}$	60	1.2
"Slow" flow	30	0

Airway Flow and Pressure; Tidal Volume.—Airway gas flow was measured with a Fleisch pneumotachograph placed between the ventilator tubing and the endotracheal or tracheostomy tube. The flow signal was integrated electronically (Hewlett-Packard Respiratory Preamplifier—Model 350-5000) to measure inspired and expired gas volume. Airway pressure was measured with an appropriate pressure transducer (Hewlett-Packard 270 with 350-1100 Carrier Preamplifier) placed immediately proximal to the endotracheal tube. Airway pressure, flow, and volume were recorded simultaneously on a multichannel recorder.*

Characteristic flow and pressure configurations for each pattern are shown in figure 1. As EIP was instituted, peak inspiratory pressure (PIP) fell to a plateau level, referred to as the plateau pressure or end-inspiratory plateau pressure (EIPP). Inspiratory to expiratory (I/E) time ratio was determined from the chart record of the inspiratory-expiratory flow rates. The zero flow period (EIP) was considered to be part of the inspiratory time in the calculation of the I/E ratio.

Compliance.—Total compliance (C_T) was calculated at end of inspiration in the control and "slow" flow patterns and at end of the zero flow period in both EIP patterns. Due to the different inspiratory flow rates and the addition of EIP to certain patterns, IP varied; thus, the compliance values obtained were differentiated into dynamic, effective, and plateau compliances (see Appendix).

Arterial Blood Gases.—At the end of each study period, arterial P_{O_2}, P_{CO_2}, and pH values were determined with appropriate electrodes. The alveolar-arterial O_2 tension difference on 50% O_2 ($AaDO_2^{0.5}$) was calculated using the alveolar air equation[7] (see Appendix).

*Sanborn System, #964-1100.

Dead-Space Ventilation.—The physiologic dead-space to tidal-volume ratio (V_D/V_T) was determined by the Enghoff modification of the Bohr equation. Appropriate corrections for compressible volume (V_{comp}) and apparatus dead space ($V_D$app) were included and are shown in the appendix. Carbon dioxide production ($\dot{V}CO_2$) was determined during each study period.

Cardiac Output was measured in duplicate by the dye-dilution technic during the final minutes of the 2nd control period and during the $EIP_{1.2}$ pattern.

Functional Residual Capacity (FRC) was measured in 5 patients using the standard helium dilution technic.

Statistical analysis of each study pattern and preceding control was carried out using Student's *t*-test paired data, to determine significant differences in $AaDO_2^{0.5}$, V_D/V_T, $Paco_2$, $F\bar{E}co_2$, $\dot{V}co_2$, and cardiac output. Values were considered significant at the $p<0.05$ level.

RESULTS

Mean values for $AaDO_2^{0.5}$, $Paco_2$, V_D/V_T, $F\bar{E}co_2$, and $\dot{V}co_2$ during each ventilation period are shown in table 4. Results during the 4 control periods were quite similar, such that the initial control condition was always reestablished following each study pattern. The effect of each pattern on gas exchange was evaluated by comparing it with the preceding control. No appreciable changes were observed in heart rate, blood pressure, CVP, or urine output. Oxygenation ($AaDO_2^{0.5}$) remained unchanged with EIP and with "slow" flow patterns when compared with control values. Efficiency of ventilation improved with institution of EIP (fig 2). With $EIP_{0.6}$ mean V_D/V_T decreased by 9.6% and mean $Paco_2$ by 5.1%. $EIP_{1.2}$ produced a further decrease in mean V_D/V_T (19.6%) and in mean $Paco_2$ (9.7%). The "slow" flow pattern failed to improve the distribution of ventilation, as evidenced by lack of changes in either V_D/V_T or $Paco_2$. Carbon dioxide production and $F\bar{E}co_2$ (corrected for compressible volume) were not significantly changed during each of the different study patterns when compared with the preceding control. Mean cardiac output decreased by 10% with $EIP_{1.2}$ (range −23% to +2.3%).

Mean airway pressure (MAP) increased with the institution of EIP and with the "slow" flow pattern, due to prolongation of the inspiratory period (table 5); MAP was

TABLE 4
Effect of Ventilatory Pattern on Oxygenation ($AaDO_2^{0.5}$), Ventilation (V_D/V_T, $Paco_2$, $F\bar{E}co_2$, $\dot{V}co_2$) and Cardiac Output (Mean Values ± SD)

	C_I	$EIP_{0.6}$	C_{II}	$EIP_{1.2}$	C_{III}	"Slow" flow	C_{IV}
$AaDO_2^{0.5}$	166 ± 54	172 ± 71	163 ± 45	170 ± 62	174 ± 48	177 ± 45	175 ± 41
$Paco_2$	39 ± 7	37 ± 6*	41 ± 8	37 ± 8†	42 ± 6	41 ± 7	41 ± 5
V_D/V_T	0.52 ± 0.08	0.47 ± 0.04	0.51 ± 0.06	0.41 ± 0.05†	0.52 ± 0.06	0.53 ± 0.07	0.51 ± 0.08
$F\bar{E}co_2$	2.5 ± 0.7	2.55 ± 0.65	2.6 ± 0.55	2.8 ± 0.75	2.55 ± 0.65	2.45 ± 0.8	2.6 ± 0.06
$\dot{V}co_2$, ml/min	233 ± 44	242 ± 58	244 ± 56	257 ± 57	239 ± 50	230 ± 45	249 ± 58
Cardiac output, L/min	—	—	5.92 ± 2.55	5.35 ± 2.3‡	—	—	—

C = control.
*$p<0.01$.
†$p<0.001$.
‡$p<0.02$.
N.B. When mean value during study pattern was compared to mean value during preceding control pattern.

TABLE 5
Changes in V_D/V_T, MAP, I/E, and Compliance Measurements with Different Ventilatory Patterns (Mean ± SD)

	Control (mean)*	$EIP_{0.6}$	$EIP_{1.2}$	"Slow" flow
V_D/V_T	0.51 ± 0.06	0.47 ± 0.04	0.41 ± 0.05	0.53 ± 0.07
MAP, cm H_2O	8.2 ± 4.1	9.9 ± 4.6	13 ± 5.8	11.1 ± 4.2
I/E	0.3 ± 0.05 (1/3.3)	0.5 ± 0.07 (1/2)	0.8 ± 0.15 (1/1.25)	0.83 ± 0.09 (1/1.2)
Compliance, ml/cm H_2O	(dynamic) 29 ± 10	(plateau) 46 ± 18	(plateau) 48 ± 17	(effective) 36 ± 13

*Represents mean values of the 4 control periods.

highest with $EIP_{1.2}$ and decreased in magnitude in the following order: $EIP_{1.2}$ > "slow" flow > $EIP_{0.6}$ >, control. Inspiratory:expiratory ratio was highest with both "slow" flow and $EIP_{1.2}$ patterns (table 5). The similarity of the mean values for I/E in the latter 2 patterns is purely coincidental. Analysis of all individual samples showed no correlation between either V_D/V_T and MAP or V_D/V_T and I/E. When "slow" flow samples were excluded, restricting the analysis to the control and the EIP patterns, a negative correlation ($r = -0.51$, $p<0.05$) was found between V_D/V_T and I/E. This implies that as I/E is prolonged with the addition of EIP (but not with "slow" flow) V_D/V_T decreases (fig 3).

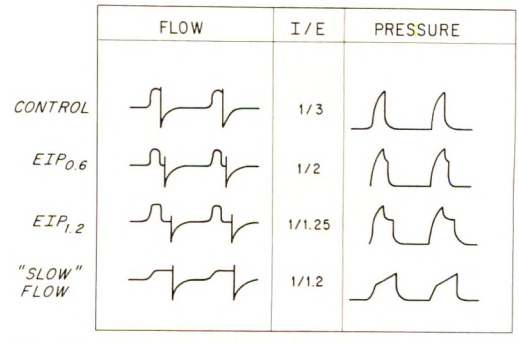


FIG 1. Airway flow, inspiratory-expiratory (I/E) time ratio, and airway pressure during ventilatory patterns.

DISCUSSION

The major findings of this study were: (1) V_D/V_T and $Paco_2$ were decreased in proportion to the duration of EIP; (2) EIP did not alter the efficiency of arterial oxygenation despite an improvement in alveolar ventilation; (3) "slow" inspiratory flow failed to change either dead-space ventilation or efficiency of oxygenation.

EIP and Hemodynamics.—The addition of EIP to ventilatory patterns prolongs I/E, sustains inspiratory pressure, and results in a higher MAP (fig 1 and table 5). An increase in mean intrathoracic pressure has been shown to impede venous return, which in the absence of compensatory mechanisms would be expected to produce a decrease in cardiac output.[8] Furthermore, sustained lung distention with increased alveolar pressure and subsequently higher transpulmonary pressure would elevate pulmonary vascular resistance, which in turn may contribute to the fall in cardiac output.[9,10] Studies in anesthetized dogs with normal lungs demonstrated a decrease in cardiac output and stroke volume with the addition of EIP.[6,9] Our results are in agreement with the preceding data. Nevertheless, despite the small decrease in cardiac output with $EIP_{1.2}$, there were no demonstrable effects on recorded vital signs, including blood pressure, heart rate, and urine output.

EIP and Oxygenation.—Previous studies with healthy dogs under general anesthesia have shown that the addition of EIP to mechanical ventilation increased room air Pao_2 and decreased calculated pulmonary shunt.[6] In dogs[11] with oleic acid-induced pulmonary edema, the addition of EIP to the ventilatory pattern had no beneficial effect on $AaDO_2$[1.0]. However, Pao_2 was significantly improved when PEEP instead of EIP was applied at a similar level of MAP.

In view of the previously suggested improvement in both alveolar ventilation and $\dot{V}_A/\dot{Q}$ by EIP, Cheney[11] postulated that the expected increase in oxygenation may have been masked in the experiment cited above because the dogs were being ventilated with

100% O_2. Patients in our study were ventilated with 50% O_2, and despite improved alveolar ventilation with EIP, there was no significant effect on oxygenation. The latter may be partially accounted for by the decrease in cardiac output, but even in patients whose cardiac output did not decrease, no improvement in oxygenation was noted. Cardiac output and $\dot{V}_A$ are not the sole determinants of Pao_2, which may be affected by the presence of pulmonary shunts and by whatever effect EIP might have upon the redistribution of cardiac output through the pulmonary vasculature. The latter phenomenon would probably affect $\dot{V}_A/\dot{Q}$, and this would require further documentation. We do not postulate that in a certain region of the lung where $\dot{V}_A$ improved following the addition of EIP, an expected regional improvement in O_2 content would occur even though this may not be reflected in the peripheral Pao_2.

EIP and Efficiency of Ventilation.—The nonhomogeneous properties of the diseased lung, for example, regional differences in compliance and airway resistance, result in uneven distribution of ventilation and thus interfere with gas exchange.[12] The Engström respirator has been designed to compensate for changes in lung mechanics, ensuring thus a most nearly equal intrapulmonary gas distribution even in the presence of unequal resistance factors.[13] Such an equilibration takes place during the static phase, when the respirator gas flow is essentially zero. At this stage, the excess volume which filled the lung was found to correspond to the available compressible volume from the respirator.[2]

In a dog model with mechanically induced unilateral bronchial obstruction, the static phase pattern of the Engström ventilator allowed for redistribution of inspired volume from nonobstructed to obstructed lung compartments.[14] Recent studies on lung models with regional differences in airway resistance revealed that EIP resulted in optimal distribution of ventilation regardless of flow rates of patterns utilized.[3,4] In a homogeneous lung model, alveolar dead space decreased as EIP was increased,[15] and in anesthetized dogs, the improvement in $\dot{V}_A$ with the institution of EIP was found to be directly proportional to the duration of added EIP.[5]

No such data have yet been collected in patients with acute respiratory disease. Our study reveals that in the latter group as well, EIP shows the same trend as was seen in lung models and experimental animals; efficiency of ventilation is improved as seen by a decreased V_D/V_T and $Paco_2$, the decrease being in proportion to the duration of EIP (fig 2).

Improved alveolar ventilation with EIP has been suggested to occur through two main mechanisms:[5] first, as in breathholding, by allowing more time for exposure of an inspired breath and therefore more unloading of CO_2 into alveoli. Calculated $V_D$phys decreases during breathholding,[16] and the effect of delaying expiration results in a higher alveolar CO_2 content than if expiration were not delayed.[15] Second, by recruitment of poorly ventilated alveoli in the presence of varying airway obstruction

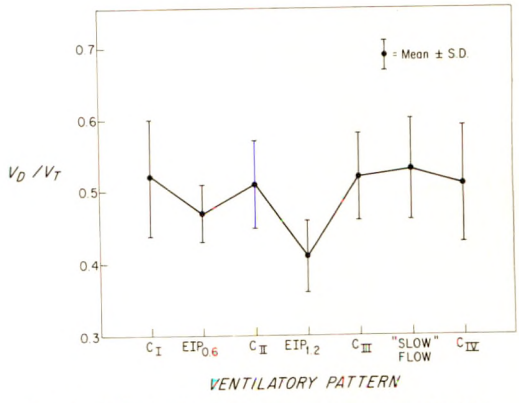


FIG 2. Effect of ventilatory pattern on V_D/V_T.

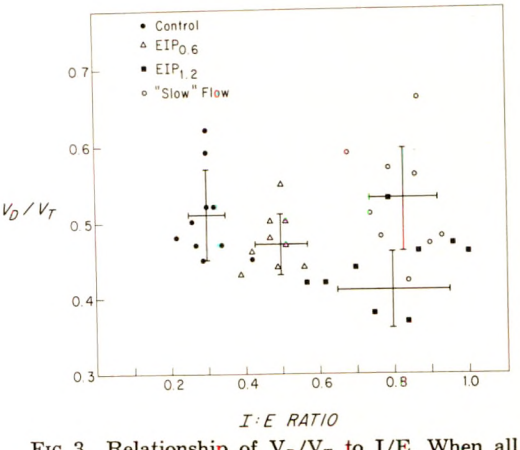


FIG 3. Relationship of V_D/V_T to I/E. When all ventilatory patterns were included, no correlation was found between V_D/V_T and I/E ($r = -0.71$). When "slow" flow samples were excluded, a negative correlation ($r = -0.51$, $p<0.05$) was found between V_D/V_T and I/E, implying a decrease in V_D/V_T as I/E is prolonged with the addition of EIP.

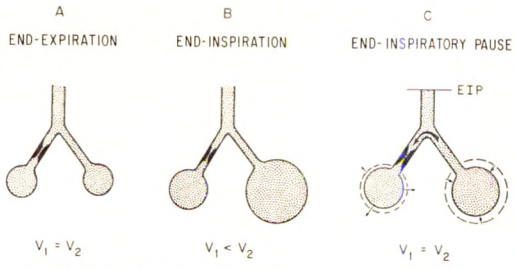


FIG 4. The effect of EIP on the distribution of ventilation in lung compartments with different airway resistances. Assuming 2 lung compartments (V_1 and V_2) with similar compliance and blood flow and an increased airway resistance in V_1 (A), then, during inspiration, the fast-filling compartment (V_2) receives the bulk of the insufflated volume (B). With EIP (C), redistribution of ventilation occurs from the fast-filling compartment (V_2) into the slow-filling compartment (V_1).

resulting in an increased effective diffusing surface and decreased $\dot{V}_A/\dot{Q}$ imbalance,[5] a mechanism illustrated in figure 4:

Assuming two lung compartments with similar compliance, equal blood flow and different airway resistances, if air is insufflated at a fast flow rate, the fast-filling compartment, that is the one with least airway resistance, would receive the bulk of the volume, resulting in an overblown compartment. This mechanism has been suggested by Norlander[2] to compress neighboring lung compartments with subsequent decrease in their compliance. If expiration is allowed to proceed immediately at the end of inspiration, no time would be provided for gas redistribution, resulting in unequal ventilation and $\dot{V}_A/\dot{Q}$ imbalance. If instead, EIP is instituted at the end of inspiration, the latter would delay expiration and would provide time for equal redistribution of ventilation and therefore improved $\dot{V}_A$ and $\dot{V}_A/\dot{Q}$ imbalance.

V_D/V_T, MAP, and I/E.—In patients without pulmonary disease, ventilation was found to be more efficient during intermittent positive-pressure breathing using high mean airway pressure.[17] In our study, changes in V_D/V_T did not correlate with changes in MAP; this is in agreement with previous findings, where V_D/V_T did not vary with MAP so long as inspiration lasted more than 1 second.[18]

As I/E was prolonged with the addition of EIP, V_D/V_T decreased. The latter did not occur when I/E was prolonged by slowing the inspired flow rate (fig 3). This indicates that it is not merely I/E, but rather how inspiratory time is utilized, that seems to influence the efficiency of ventilation. Slowing the flow rate did not improve V_D/V_T in our studies, and this is in disagreement with findings in lung models where $\dot{V}_A$ to obstructed compartments was improved with a slow flow rate.[4] Also, previous studies with patients have shown that $V_D$phys and V_D/V_T increased as $\dot{V}_{insp}$ was increased above 25 L/min, but in the latter studies, no correction for compressible volume was done, which make the results difficult to evaluate.[19]

Use of EIP in Noncompliant Lungs.—In studies on lung models with regional differences in compliance, ventilation to the poorly compliant regions was not improved with changes in flow rate and flow pattern or with the addition of EIP.[4] Therefore, it was suggested that in poorly compliant lungs, it may be more advantageous to use a rapid inspiration with volume acceleration.[3] Our data do not provide a solution as to whether EIP would have an effect on the ventilation of poorly compliant lungs. However, in patient 8, where C_T was markedly decreased (table 2), there was a significant improvement in V_D/V_T with the institution of $EIP_{1.2}$.

We conclude that this study confirms that the addition of EIP to the inspiratory flow pattern in patients with ARI produces a definite improvement in alveolar ventilation and $V_D$phys, but has no demonstrable effect on efficiency of oxygenation. This may not be of practical significance in the short-term management of patients; however, the long-term effects of maintaining EIP may result in a beneficial effect on gas exchange and pulmonary mechanics, and may provide a more nearly optimal condition for lung repair in otherwise poorly ventilated alveoli. One practical value of EIP is that it allows easy measurement of plateau compliance, a reproducible value important in the assessment and follow-up of pulmonary function in critically ill patients.

APPENDIX

I. Total Compliance (C_T) = $\triangle V$ (ml) / $\triangle P$ (cm H_2O) = V_T (recorded by pneumotachography) / IP-EEP. End-inspiratory pressure coincided with peak inspiratory pressure in the control and "slow" flow patterns and with the "plateau pressure" in both EIP patterns (fig 1). C_T as measured in the control pattern represented dynamic compliance. In the "slow" flow pattern, the

latter was referred to as effective compliance, since duration of inspiration was 2.5 to 3.1 seconds as compared to 1.2 to 1.6 seconds in the control period. C_T measured in both EIP patterns was referred to as plateau compliance.

II. $AaDO_2 = P_{AO_2} - P_{aO_2}$, where $P_{AO_2} = P_{IO_2} - P_{ACO_2}\left(F_{IO_2} + \frac{1 - F_{IO_2}}{R}\right)$.

P_{ACO_2} was assumed to be equal to P_{aCO_2} and R (respiratory quotient) was assumed to be constant at a value of 0.8. This assumption introduces an element of uncertainty but is considered justified since the patients were investigated in a quasi-steady state.

III. V_D/V_T was calculated according to the standard formula:

$$V_D/V_T = \frac{P_{aCO_2} - P\bar{E}CO_2}{P_{aCO_2}} \text{ (corrected)}.$$

Expired gas was collected into a 60 L Douglas bag at the end of each ventilatory pattern during a 3-minute period. Expired gas volume was measured with a Tissot spirometer and corrected to BTPS. Mixed expired CO_2 concentration ($F\bar{E}CO_2$) was determined with an infrared CO_2 analyzer (Beckman Model LB-1) and $P\bar{E}CO_2$ was derived as follows: $P\bar{E}CO_2 = F\bar{E}CO_2 (P_B - P_{H_2O^T})$. $P\bar{E}CO_2$ was corrected for both the compressible volume of the ventilator tubing (3.5 ml/cm H_2O) and the effect of added apparatus dead space. To correct for compressible volume, end-inspiratory pressure was used in the same manner as described for the compliance measurements (appendix, I).

Based on previous physiologic considerations[20] that in the presence of unperfused alveoli, the increase in physiologic dead space is constantly smaller than the size of added apparatus dead space, the formula ($V_D phys = V_D m - 0.5\ V_D app$) seems more appropriate than the conventional $V_D phys = V_D m - V_D app$. The latter would actually result in an underestimation of physiologic dead space. A similar corrected value of $V_D phys$ may be approximated through the following equation:*

$$V_D/V_T = \frac{P_{aCO_2} - P\bar{E}CO_2\left(\frac{V_T}{V_T - V_{comp} - 0.5\ V_D app}\right)}{P_{aCO_2}}$$

NB: Because of some variation in the value of V_T measured with the Tissot spirometer or with the pneumotachograph, both values were used in calculating V_D/V_T. The difference in V_D/V_T calculated according to both methods was negligible (0 ± 0.02 at most). The reported figure is the average of both numbers.

IV. $\dot{V}CO_2 = V_T$ (measured with the Tissot spirometer and corrected for BTPS) $\times$ respiratory rate $\times F\bar{E}CO_2$.

*Our computation.

REFERENCES

1. Ingelstedt S, Jonson B, Nordstrom L, et al: A servo-controlled ventilator measuring expired minute volume, airway flow and pressure. Acta Anaesthesiol Scand 16 (suppl 47):7-27, 1972

2. Norlander OP: The use of respirators in anaesthesia and surgery. Acta Anaesthesiol Scand 12 (suppl 30):5-74, 1968

3. Lyager S: Influence of flow pattern on the distribution of respiratory air during intermittent positive-pressure ventilation. Acta Anaesthesiol Scand 12:191-211, 1968

4. Jansson L, Jonson B: A theoretical study on flow patterns of ventilators. Scand J Respir Dis 53:237-246, 1972

5. Knelson JH, Howatt WF, DeMuth GR: Effect of respiratory pattern on alveolar gas exchange. J Appl Physiol 29:328-331, 1970

6. Lyager S: Ventilation/perfusion ratio during intermittent positive-pressure ventilation. Acta Anaesthesiol Scand 14:211-232, 1970

7. Comroe JH, Forster RE, DuBois AB, et al: The Lung. Second edition. Chicago, Year Book Medical Publishers, Inc, 1962, pp 339-341

8. Cournand A, Motley HL, Werko L, et al: Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. Am J Physiol 152:162-174, 1948

9. Nordstrom L: Haemodynamic effects of intermittent positive-pressure ventilation with and without end-inspiratory pause. Acta Anaesthesiol Scand 16 (suppl 47):29-56, 1972

10. Adams AP, Economides AP, Finlay WE, et al: The effects of variations of inspiratory flow waveform on cardiorespiratory function during controlled ventilation in normo-, hypo- and hypervolemic dogs. Br J Anaesth 42:818-825, 1970

11. Cheney FW, Burnham SC: Effect of ventilatory pattern on oxygenation in pulmonary edema. J Appl Physiol 31:909-912, 1971

12. Otis AB, McKerrow CB, Bartlett RG, et al: Mechanical factors in distribution of pulmonary ventilation. J Appl Physiol 8:427-443, 1956

13. Engström CG: The clinical application of prolonged controlled ventilation. Acta Anaesthesiol Scand 7 (suppl 13):7-50, 1963

14. Sabar EF, Norlander O, Osborn J, et al: Gas distribution studies in experimental unilateral bronchial constriction using an accelerating-flow, volume-controlled respirator. Surgery 58:713-719, 1965

15. Nye RE: Influence of the cyclical pattern of ventilatory flow on pulmonary gas exchange. Respir Physiol 10:321-337, 1970

16. Bartels J, Severinghaus JW, Forster RE, et al: The respiratory dead space measured by single breath analysis oxygen, carbon dioxide, nitrogen or helium. J Clin Invest 33:41-48, 1954

17. Bergman NA: Effect of different pressure breathing patterns on alveolar-arterial gas gradients in dogs. J Appl Physiol 18:1049-1052, 1963

18. Bergman NA: Effects of varying respiratory waveforms on gas exchange. Anesthesiology 28:390-395, 1967

19. Fairley HB, Blenkarn GD: Effect on pulmonary gas exchange of variations in inspiratory flow rate during intermittent positive-pressure ventilation. Br J Anaesth 38:320-328, 1966

20. Suwa K, Bendixen HH: A mathematical analysis of physiological dead space in a lung model. J Appl Physiol 24:549-555, 1968

Guest Discussion

JOHN B. DOWNS, M.D.
Department of Anesthesiology
University of Florida
College of Medicine
Gainesville, Florida

The authors demonstrated increased efficiency of alveolar ventilation when an end-inspiratory pause (EIP) was added to the mechanical ventilatory pattern of patients with acute respiratory insufficiency. Based on this observation, it might seem desirable to introduce such a mechanical ventilatory pattern to the therapeutic regimen of patients with excessive CO_2 retention. However, positive pressure ventilation which will increase mean airway pressure, mean intrapleural pressure, and to a lesser extent left atrial pressure, may decrease diastolic filling of the left ventricle and cardiac output. Thus, EIP may exaggerate the adverse hemodynamic effects of mechanical ventilation.

The observed increase in alveolar ventilation following addition of EIP would be most beneficial for patients with hypercarbia. Such patients frequently have marked obstructive lung disease or severe hypovolemia and increased physiologic dead space. Unfortunately, the cardiovascular effects of EIP would be tolerated least by such patients. In most patients who require mechanical ventilator support, CO_2 elimination can be enhanced by a slight increase in tidal volume or ventilator rate. Since hypocarbia is more common than hypercarbia in patients receiving mechanical ventilatory therapy, addition of EIP may be desirable only in select cases.

Recently, other investigators[1] found plateau compliance to correlate positively with systemic O_2 transport and, therefore, recommended that plateau compliance be used as an indicator of pulmonary function in patients with acute pulmonary failure. The present authors' data do not support this premise. The $AaDO_2^{0.5}$ did not correlate negatively with plateau compliance, as might have been predicted (tables 2 and 4). Since cardiac output was reduced significantly following addition of EIP, there must have been a significant decrease in systemic O_2 transport. This implies that pulmonary mechanics and gas exchange should be evaluated independently in patients with acute respiratory insufficiency.

The authors are to be congratulated for providing reliable information obtained from well-controlled measurements in patients with respiratory insufficiency rather than in lung analogs, animals, or patients undergoing general anesthesia. As Dr. Bergman wrote,[2] "The lungs are composed, in part, of 300,000,000 alveoli together with extremely complex systems of conducting tubes for both gas and blood and are enclosed in a unique container. Their function cannot be studied by observing the inflation of two rubber bags at the end of a Y-piece."

Hopefully, manufacturers will await the results of pertinent investigations such as Dr. Fuleihan's prior to marketing expensive machines capable of providing multiple inspiratory and expiratory pressure-flow patterns which may or may not have clinical efficacy.

REFERENCES

1. Suter PM, Fairley HB, Isenberg MD: Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 292: 284-289, 1975

2. Bergman NA: Effects of varying respiratory waveforms on gas exchange. Anesthesiology 28:390-395, 1967

Questions and Answers

We invite you to submit questions to the Editorial Office, Kahler East, Suite C, Rochester, Minnesota 55901. The names of those submitting questions will remain anonymous if so desired.

The answers will be prepared by competent authorities, and their names will or will not appear, according to their specific wishes.

Ronald W. Dunbar, M.D.
Contributing Editor
Atlanta, Georgia

* * *

QUESTION: *I find the word "torr" used increasingly in place of mm Hg. What is the origin of this word, and is it an exact synonym for mm Hg?*

M.D., Illinois

ANSWER: "Torr" derives from the name of the inventor of the mercury barometer, Evangelista Torricelli, an Italian physicist-mathematician (1608-1647). Early Hg barometers were known as Torricelli tubes. Because "torr" is a more convenient term than mm Hg typographically, it has been widely accepted in scientific literature.

Strictly, 1 torr is 1 mm Hg pressure equal to $\frac{1}{760}$ of normal atmospheric pressure (1.316×10^{-3} atm), or the pressure necessary to support a column of mercury 1 mm high at 0° C and standard gravity.[1,2] Usage has made the term generally acceptable as a synonym for mm Hg at ambient or clinical temperatures, as well.

REFERENCES

1. Dorland's Illustrated Medical Dictionary, 25th Edition, Philadelphia, WB Saunders Company, 1974

2. The American Heritage Dictionary of the English Language, American Heritage Publishing Co, 1969

* * *

QUESTION: *What is the present status of intrathecal cold saline solution for intractable pain, primarily of adenocarcinoma?*

M.D., Kansas

ANSWER #1: Encouraging results with the use of intrathecal cold saline were reported not only by Collins and associates[1] but also more recently by Savitz and Malis.[2] Many clinicians, however, have not been able to duplicate the results obtained by these authors. A number of clinics, including our own, are now evaluating the use of intrathecal hypertonic saline (7.5 percent) for the relief of intractable pain, as described by Hitchcock.[3] Both these technics are attractive because relief of pain is achieved without producing sensory anesthesia. It should be noted, however, that the procedure is not without definite risks.

In a recent questionnaire circulated among neurosurgeons using the injection of hypertonic saline for debilitating pain syndromes, a small but significant morbidity was noted, of which the most common, paraplegia or quadraplegia, occurred in 0.05 percent of the total patient population (2000). Other significant morbidity consisted of paresis of one leg, myocardial infarction, and cerebrovascular accident. In summary, I think that the injection of intrathecal saline for the relief of intractable pain requires further clinical evaluation before its relative place vis-a-vis standard forms of treatment of intractable pain secondary to carcinoma (drug therapy, chordotomy, intrathecal alcohol) can be established.

REFERENCES

1. Collins JK, Juras EP, VanHouten RJ, et al: Intrathecal Cold Saline Solution: A New Approach to Pain (Evaluation). Anesth & Analg 48:816-822, 1969

2. Savitz MH, Malis LI: Intrathecal injection of isotonic iced saline for intractable pain. Mount Sinai J Med 39:134-145, 1972

3. Hitchcock E: Osmolytic neurolysis of intractable facial pain. Lancet 1:434-436, 1969

Eli M. Brown, M.D.
Department of Anesthesiology
Sinai Hospital of Detroit
Detroit, Michigan

ANSWER #2: The use of intrathecal cold saline has decreased in my practice for three reasons:

1. The belief that it was not the cold that was providing the pain relief but the hypertonicity of the solution.

2. My practice has changed in that I no longer see many battle casualties with causalgia.

3. The effectiveness in cancer patients is only temporary and has not been recommended by me in treatment of cancer pain.

I have used the method with moderate success in patients with post-herpetic neuralgia. Also I have used the technic in paraplegics and amputees with phantom pain and/or sympathetic reflex dystrophy.

At the time I was actively using the technic, other individuals were using hypertonic saline, that is, 5 and 10 percent solutions at room temperature, with comparable results.

The question is vague, in that I don't know the site of the cancer or the nature of the pain. If the pain is that of adenocarcinoma of the bowel, it would seem to me that a splanchnic plexus block would be more effective. Intrathecal cold saline is one of the means we consider in our course of pain therapy; however, as I mentioned above, our use of this technic has decreased.

Jack R. Collins, M.D.
Department of Anesthesiology
The Jewish Hospital of
St. Louis
St. Louis, Missouri

* * *

QUESTION: *Do you have any experience with prolonged continuous epidural for postoperative patients in the treatment of pain? How long can you keep the catheters safely? What is your experience on fractional doses of antibiotics injected into the epidural catheter to keep it clean and sterile? Please furnish me with some references and literature about epidural antibiotics with prolonged catheterization.*

M.D., Maryland

ANSWER #1: Continuous epidural anesthesia for postoperative pain relief can be a useful substitute for narcotics in specific patients following abdominal surgery.[1-4] Several reports have documented this fact and those who advocate its frequent use can show that patients will maintain more normal pulmonary function,[5,6] recover faster,[2] and perhaps be more comfortable.[5] The limited popularity of this method of pain relief is undoubtedly related to the fact that it can be time consuming and usually demands the attention of the physician for repeated injections. The busy and beleaguered anesthesiologist would rather resort to the more common canon of parenteral narcotics for postoperative analgesia, with the pious conviction that the patient will do just as well.

In an effort to establish prolonged postoperative pain relief or chronic sympathetic block, I have left epidural catheters in place as long as a week. Others report as many as 10 days.[7] The tachyphylaxis which frequently develops following multiple injections of local anesthetics will very often limit the useful life of a continuous epidural to a much shorter time.[8] However, as long as the catheter fulfills the purpose for which it was put in place, I see no reason to remove it because of some arbitrary time factor.

The epidural abscess is a disastrous condition which can occur spontaneously, result from trauma,[9] or follow lumbar and caudal instrumentation. It does, however, seem to rank very low among the possible complications of epidural anesthesia. In one study aimed at looking into the potential for epidural infection, several cultures of catheter tips, solutions, and even the surrounding skin were found to be virtually free of bacteria.[7] The authors, however, were very scrupulous with methods of introducing the catheter and its protection after it was in place.

Based on these facts, I would question the wisdom or the need for a prophylactic treatment method such as injecting into an epidural catheter fractional doses of antibiotics, when the apparent incidence of infection is so low. Another consideration is the fact that the antibiotic itself might be harmful to the nerve root because of such factors as osmolarity, pH, or chemical toxicity. I know of no one who uses prophylactic antibiotics and I would personally have serious reservations about the need or the safety of such a practice.

REFERENCES

1. Collie JA: Epidural analgesia for postoperative pain relief. Proc Roy Soc Med 67:59, 1974

2. Pflug AE, Murphy TM, Butler SH, et al: The effects of postoperative peridural analgesia on

pulmonary therapy and pulmonary complications. Anesthesiology 41:8, 1974

3. Saha AK, Singh A: Postoperative pain relief and the monoamine oxidase inhibitors. Anaesthesia 28:467-468, 1973

4. Sjogren S, Wright B: Circulation, respiration and lidocaine concentration during continuous epidural blockade. Acta Anaesth Scand Suppl 46:27-49, 1972

5. Spence AA, Smith G: Postoperative analgesia and lung function: a comparison of morphine with extradural block. Brit J Anaesth 43:144-148, 1971

6. Hollmen A, Saukkonen J: The effects of postoperative epidural analgesia versus centrally acting opiate on physiological shunt after upper abdominal operation. Acta Anaesth Scand 16:147-154, 1972

7. Barreto RS: Bacteriological culture of indwelling epidural catheters. Anesthesiology 23:643-646, 1962

8. Cohen EN: The role of pH in the development of tachyphylaxis to local anesthetic agents. Anesthesiology 29:994-1001, 1968

9. Hulme A, Dott NM: Spinal epidural abscess. Br Med J 1:64-68, 1954

Col. Francis J. Dannemiller
Department of Anesthesiology
Wilford Hall USAF Medical Center
Lackland Air Force Base, Texas

ANSWER #2: To answer this important question, I will report on the use of continuous epidural analgesia for both postoperative pain and chronic pain states. For the purpose of description, these will be divided into two groups, the first consisting of 600 cases in which the epidural catheter was left in situ for a mean duration of 28 hours. The second group of 27 cases, being managed for various chronic pain states, will be further subdivided into short (7), medium (11), and long (6) periods. The mean duration of catheterization in these groups was, respectively, 2.5, 3.4, and 5.7 days. Three patients were blocked for 9, 11, and 18 days, respectively. These three cases represent an extreme application of this technic, which was an adjunct to concurrent hypno- and psychotherapy. They illustrate what may be a fundamental property of the epidural space, namely resistance to infection, presumably through the great vascularity contributed by the internal vertebral venous plexus together with its segmental connections, which has been adequately described by Batson.[1]

In addition, there is good evidence that local anesthetics are, if not bactericidal, bacteriostatic. A good account of the antimicrobial activity of lidocaine and procaine is given by Schmidt and Rosenkranz,[2] who testify to the broad spectrum of bactericidal activity of these two local anesthetics. Earlier literature by Murphy and his colleagues[3] describes the toxic effects of 0.5 percent solution of tetracaine on Pseudomonas organisms. These two papers suggest that this property may be shared by other anilide types of local anesthetics currently in use.

I have no experience in the use of fractional doses of antibiotics, and the literature is singularly void of any references in this regard. However, there seems little argument in favor of prophylactic administration of epidural antibiotics. In fact, on first principles, even in the presence of an infection, it would appear more appropriate to give parenteral antibiotics. Also, one should remember that some antibiotics, notably penicillin and streptomycin, can give rise to convulsions when applied to the spinal theca. An account by Bordbar and Beheshti[4] of two such cases appeared recently, and reference to this effect is also made by Goodman and Gilman.[5]

I advocate the use of long-term epidural block for the control of pain either in the postoperative period or in pain states, provided an aseptic technic is followed during each reinjection and provided modern inert (nylon or Teflon) catheters are used, with or without a micropore filter; then there is no argument in favor of using epidural antibiotics.

REFERENCES

1. Batson OV: The function of the vertebral veins and their role in the spread of metastases. Ann Surg 112:138-149, 1940

2. Schmidt RM, Rosenkranz HS: Antimicrobial activity of local anesthetics: lidocaine and procaine. J Infect Dis 121:597-607, 1970

3. Murphy JT, Allen HF, Mangiaracine AB: Preparation, sterilization and preservation of ophthalmic solutions. Experimental studies and a practical method. Arch Ophthal 53:63-78, 1955

4. Bordbar A, Beheshti M: Postoperative convulsions due to penicillin applied to the spinal theca. Anaesthesia 30:56-58, 1975

5. Goodman LS, Gilman A: The Pharmacological Basis of Therapeutics. Fourth edition. New York, 1973, p 1215

Michael d'Arcy Stanton-Hicks, M.D.
Department of Anaesthesiology
University of Massachusetts Medical Center
Worcester, Massachusetts

QUESTION: *The Joint Commission on Hospital Accreditation demands that the humidity of the operating room be kept at 55%. We realize this was done to reduce the explosion hazards where explosive anesthetic agents were in use. In our operating rooms, we do not use explosive anesthetics or combustible prepping solutions (spray tc of benzoin being the only flammable agent in use). We find it difficult to maintain 55% humidity and twice have been cited by the Joint Commission for this.*

We see no need for 55% humidity, but only 30 to 35% humidity for comfort control. This seems to be an archaic rule that is not necessary where explosive agents are not in use, but we cannot convince the Joint Commission.

Are we wrong, or should the Joint Commission accept 30 to 35% humidity where explosive anesthetics are not in use and rooms are air conditioned and conductive floors exist?

M.D., Ohio

ANSWER: At a meeting of the ASA Committee on Flammable Hazards and Electrical Equipment, May 14, 1975, the consensus of the Committee was that 50% humidity was still desirable for: (1) control of static electricity (startle reaction); (2) comfort of personnel; and (3) to facilitate the control of airborne bacteria. This requirement was felt to be important for nonflammable as well as flammable anesthetizing locations.

Currently, the JCAH recommends in the Accreditation Manual for Hospitals (1970, updated 1973) that NFPA 56A 1968 should be used as a guide in establishing controls to minimize the hazards of fire and explosion in areas where flammable anesthetics are used; also, that NFPA Standards should be used to develop regulations relative to anesthetic safety (see JCAH Manual, pp 62 and 85). NFPA 56A 1973 is the latest edition of the Standard for the Use of Inhalation Anesthetics and still states that "a relative humidity of not less than 50% at a temperature range of 70° ± 5° F, shall be maintained in anesthetizing locations, both flammable and nonflammable."

The NFPA Sectional Committee on Anesthetizing Agents, which is responsible for the NFPA 56A Standard, met in Cleveland on July 11, 1975, and agreed to review this requirement at their next meeting.

James A. Meyer, M.D.
Chairman, ASA Committee on
Flammable Hazards and
Electrical Equipment
ASA Delegate to the NFPA
Letterman Army Medical Center
San Francisco, California

AWAKE DURING OPERATION Awareness during anesthesia and operation may result in a traumatic neurotic syndrome. The authors describe such a syndrome in six patients characterized by 1) recurrent nightmares, 2) irritability, 3) a preoccupation with death, and 4) reluctance to describe symptoms to physicians for fear they would be misinterpreted. In all six cases a direct explanation to the patient that they indeed were "awake" during the operation served as a dramatic cure. The incidence of such occurrences may be underestimated due to patient reluctance to discuss their symptoms. *(Blacher RS: On awakening paralyzed during surgery. A syndrome of traumatic neurosis. JAMA 234:67-68, 1975)*

Hemodynamic Effects of Isoflurane and Halothane in Patients with Coronary Artery Disease

JAMES E. MALLOW, M D *
ROGER D. WHITE, M D †
ROY F. CUCCHIARA, M D †
SAIT TARHAN, M D †
Rochester, Minnesota‖

In 12 patients undergoing saphenous vein coronary artery bypass operations, cardiovascular hemodynamics were studied in the awake state (control) and during anesthesia with isoflurane (inspired concentration, 1.24%, 7 patients) or with halothane (inspired concentration, 0.77%, 5 patients). Isoflurane anesthesia was accompanied by decreases of 19% in the cardiac index ($\dot{Q}$), 19% in mean arterial pressure ($\overline{AP}$), and 16% in heart rate (HR). Only the change in $\overline{AP}$ was statistically significant. Halothane anesthesia was accompanied by decreases in $\dot{Q}$ (28%), $\overline{AP}$ (22%), and HR (10%). The changes in $\dot{Q}$ and $\overline{AP}$ were significant. HR did not change significantly following the induction of anesthesia with either agent. The decrease in $\overline{AP}$ was similar with both agents, and, in this regard, neither agent was clearly superior for patients with occlusive coronary artery disease.

RECENT studies have suggested several advantages of isoflurane anesthesia as compared with halothane anesthesia in man. These have included the absence of sensitization of myocardium to exogenously administered epinephrine;[1] minimal metabolism in man;[2] lower blood-gas partition coefficient, leading to more rapid induction and emergence;[3] and better maintenance of cardiac output.[4]

The last of these reported advantages has not been documented for patients with limited cardiac function. Accordingly, we designed a clinical study of patients with coronary artery disease (CAD), to determine whether isoflurane anesthesia would maintain cardiovascular hemodynamics better than halothane anesthesia at equivalent minimum alveolar concentrations (MAC).¶ Patients were selected at random and anesthetized with either isoflurane or halothane in O_2. Cardiovascular hemodynamics were measured in the awake and anesthetized states with each agent, and the hemodynamic changes produced by the two anesthetics were compared.

METHODS

The study group comprised 12 patients without clinical evidence of pulmonary disease, scheduled for saphenous vein bypass grafting for CAD. All patients were New York Heart Association class III and were premedicated with diazepam (10 mg) and morphine sulfate (6 to 8 mg) IM 1 hour before study. Seven patients were anesthetized with isoflurane [3 single-vessel (LAD), 3 double-vessel, 1 triple-vessel disease, 0 ventricular dyskinesia] and 5 with halothane [1 single-vessel (LAD), 2 double vessel, 2 triple-vessel disease, 0 ventricular dyskinesia]. In the isoflurane group, the average age was 54 years and surface area was

¶In man, the MAC of isoflurane in O_2 is $\pm 1.24\%$[3] and of halothane in O_2 $\pm 0.77\%$.[5]

*Resident.
†Assistant Professor.
‖Department of Anesthesiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901.
This study was supported in part by a grant-in-aid from Ohio Medical Products, a division of Airco, Inc.
Reprint address: Section of Publications, Mayo Clinic, Rochester, Minnesota 55901.
Dr. Mallow's present address: St. Luke's Hospital of Kansas City, Kansas City, Missouri 64111.
Paper received: 12/5/74
Accepted for publication: 6/19/75

1.99 sq m; in the halothane group, 53 years and 1.92 sq m. Informed consent was obtained from each patient the day before operation.

Prior to induction of anesthesia, standard limb leads for ECG monitoring were attached and a CVP catheter (30-cm, 16 gauge) was inserted percutaneously into the right internal jugular vein, localized in the right atrium by ECG,[6] and connected to a Statham 23-BB strain gauge. A 75-cm Teflon catheter was placed in the descending aorta via the left femoral artery (Seldinger technique[7]) and connected to a 23-D Statham strain gauge. A thermistor probe was placed in the right axilla. Right atrial (P_{RA}) and systemic arterial pressures ($\overline{AP}$) were monitored continuously.

Cardiac output ($\dot{Q}$) was determined by the dye-dilution technique.[8] Indocyanine green* (5 mg/ml) was injected into the right atrium, arterial blood was withdrawn from the descending aorta by a Harvard pump through a Gilson cuvette (model DTL) at 10 ml/min, and the dye curve was recorded simultaneously with the ECG on a Century oscillograph recorder (model 470).

Blood gases were analyzed by withdrawing arterial blood anaerobically from the descending aorta into 5-ml plastic syringes, the dead spaces of which were filled with heparin (1000 U/ml). The syringes were immediately sealed and placed in an ice bath. Pao_2, $Paco_2$, PH, and hemoglobin (hgb) were determined for each sample (37° C; Radiometer electrodes model PHM 27 and Co-Oximeter IL model 182) within 10 minutes of blood withdrawal. Standard bicarbonate was calculated with a Severinghaus slide rule.

After placement of all sensors, the awake subjects inspired 100% O_2 (nonrebreathing system) for 10 minutes. Measurements were then obtained in the following sequence:

1. arterial blood sample
2. axillary temperature
3. $\overline{AP}$ and P_{RA} measured during three respiratory cycles
4. $\dot{Q}$ followed by repeat determinations of $\overline{AP}$ and P_{RA}, axillary temperature, and arterial blood sample.

The ECG was recorded continuously. This sequence was repeated until the results of two cardiac outputs in sequence varied by less than 10%.

Induction was with either isoflurane (1.5 to 5%) or halothane (1 to 2.5%) in O_2. Endotracheal intubation with a soft-cuffed endotracheal tube was facilitated with succinylcholine (100 mg IV). For maintenance, a constant inspired concentration of isoflurane (1.24%) or halothane (0.77%) in O_2 was administered from a calibrated Fluotec® Mark II vaporizer. Each patient was mechanically ventilated at a respiratory frequency of 16/min and a tidal volume of 0.47 to 0.52 L. Tidal volume was delivered via an Engstrom Respiratory System (model ER311) with peak airway pressures of 12 to 15 cm H_2O.

After 15 minutes at the respective constant inspired concentrations and prior to the scheduled surgical procedure, all measurements were repeated in the same sequence. Blood lost through sampling (average, 100 ml) was not replaced.

Statistical comparisons of the differences between the two groups of patients were made using Hotelling's *t*-squared test (unpaired data), and comparisons of the differences between the awake and anesthetized states were made by Student's *t*-test (paired data). Comparisons were accepted as significantly different when $p<0.05$.

RESULTS

Values relating to the awake state for the isoflurane and halothane groups did not differ significantly (table). In addition, the values for hgb, standard bicarbonate, and body temperature were 14.9 gm/dl, 23.3 mEq/L, and 35.5° C, respectively, for the isoflurane group and 15.6 gm/dl, 24.6 mEq/L, and 36° C, respectively, for the halothane group. These values did not change significantly after induction of anesthesia.

Induction with isoflurane was associated with a significant change in systemic $\overline{AP}$, $Paco_2$, and pH (table). The decrease in $\overline{AP}$ was not associated with a significant decrease in either $\dot{Q}$ or systemic vascular resistance (SVR). $Paco_2$ decreased and pH increased by the same degree, due to mild hyperventilation in both groups. Induction of anesthesia with halothane was accompanied by a significant decrease of $\overline{AP}$, $\dot{Q}$, stroke volume index (SVI), and $Paco_2$ (table). The decrease in $\overline{AP}$ was paralleled

*Indocyanine green dye supplied by Hynson, Westcott and Dunning, Inc., Baltimore, Maryland.

TABLE 1
Comparisons of Hemodynamic and Respiratory Variables in Waking State and in Anesthesia With Isoflurane and Halothane

Variable	Isoflurane (N = 7)		Halothane (N = 5)	
	Awake Mean ± SE	Isoflurane (inspired concentration, 1.24%) Mean ± SE	Awake Mean ± SE	Halothane (inspired concentration, 0.77%) Mean ± SE
Cardiac index (liter/min/m^2)	2.31 ± 0.27	2.03 ± 0.28	2.94 ± 0.32	2.13 ± 0.29*
Stroke index (ml/m^2)	35 ± 3	31 ± 3	39 ± 1	31 ± 1*
Heart rate (beats/min)	71 ± 12	60 ± 4	75 ± 6	68 ± 8
Right atrial pressure (mm Hg)	6.7 ± 1.2	8.4 ± 0.7	5.5 ± 0.7	6.5 ± 1.2
Mean arterial pressure (mm Hg)	97 ± 4	79 ± 5*	96 ± 3	75 ± 3*
Systemic vascular resistance (dyne-sec/cm^{-5})	1686 ± 184	1678 ± 224	1374 ± 160	1414 ± 120
Pa_{O_2} (mm Hg)	421 ± 18	384 ± 23	483 ± 16	477 ± 22
Pa_{CO_2} (mm Hg)	41 ± 1	35 ± 2*	40 ± 1	33 ± 3*
pH	7.37 ± 0.06	7.41 ± 0.02*	7.39 ± 0.01	7.46 ± 0.02*

*Significantly different from value for waking state ($p < 0.05$).

by a decrease in $\dot{Q}$ and SVI; SVR did not change.

The decrease in $\overline{AP}$ from the awake to the anesthetized state in the isoflurane groups was not significantly different from the decrease measured in the halothane group (table).

Because of the relatively small number of patients studied and the wide individual variation in values for $\dot{Q}$, no significant difference in $\dot{Q}$ between the halothane and isoflurane groups was achieved (unpaired *t*-test), even though, as compared to their respective controls, a significant decrease occurred only in the halothane group (paired *t*-test).

HR did not change significantly from the control to the anesthetized state in either group, nor was there a significant difference in HR associated with isoflurane as compared to halothane.

DISCUSSION

A comparison between the cardiovascular effect of isoflurane and halothane anesthesia might be altered by three factors: (1) differences in $Paco_2$ and mechanical ventilation; (2) differences in MAC equivalents of isoflurane and halothane; (3) differences in the cardiovascular effects of isoflurane.

We consider it unlikely that the hemodynamic effects on these two groups can be accounted for by ventilatory differences, because respiratory frequency, tidal volume, peak airway pressure, and hypocapnia were of the same order for both groups.

The difference in MAC equivalents also seems unlikely as an explanation. Measurements were obtained in the anesthetized state after the patients had received a constant inspiratory concentration of isoflurane or halothane in O_2 for 15 minutes, preceded by induction of anesthesia with isoflurane (1.5 to 3.5%) and halothane (1 to 2.5%) for 5 minutes. Although the alveolar partial pressure of isoflurane may be expected to have increased at a faster rate than that of halothane when administered at a constant inspiratory concentration, we assume that MAC equivalents of isoflurane and halothane existed at the time the measurements were obtained. This assumption is supported by the data published by Cromwell's group[3] and by Rehder and colleagues.[9]

Rehder determined the ratio of expired to inspired halothane (F_{EHa}/F_{IHa}) in man to be 0.55, 0.69, and 0.75 after 15, 30, and 75 minutes, respectively, of exposure to a constant inspired halothane concentration, while Cromwell reported the ratio of expired to inspired isoflurane (F_{EI}/F_{II}) in man to be 0.62, 0.7, and 0.73 after 16, 32, and 64 minutes, respectively, of exposure to a constant inspired concentration. As the F_{EHa}/F_{IHa} and the F_{EI}/F_{II} are equal at 30 and 32 minutes, we believe that MAC equivalents of halothane and isoflurane were

nearly equal at the end of 20 minutes and that, therefore, a comparison of two agents is valid.

HR did not increase under isoflurane anesthesia in our patients, in contrast to the data published by Stevens and associates.[4] Similarly, no increase in HR (5 volunteers anesthetized with inspired isoflurane concentrations of 1 and 2%) from the awake to the anesthetized state was reported by Rehder in a later study.[10]

Patients with CAD, particularly those in whom the stenotic lesions of the coronary arteries are of fixed diameter, require careful management during general anesthesia to prevent acute myocardial ischemia. Ischemia occurs when the myocardial O_2 consumption ($M\dot{V}o_2$) exceeds the supply of O_2 delivered to the myocardium via the coronary arteries. A partially occluded coronary artery is associated with a pressure gradient across the stenotic area and with maximal dilation of the coronary artery distally.[11]

Under these conditions, coronary artery blood flow distal to the stenosis would be dependent primarily on aortic diastolic pressure;[12] and hence coronary blood flow then becomes essentially pressure-dependent. In patients with occlusive CAD, there is apparently an optimal aortic pressure[13] above or below which the balance between myocardial O_2 supply and demand is upset and acute myocardial ischemia results. The intraoperative development of acute myocardial ischemia secondary to hypotension without a proportionate reduction in $M\dot{V}o_2$ is manifested on the ECG by displacement of the ST segment.

In both of our groups, $\overline{AP}$ decreased significantly; the decrease with isoflurane anesthesia was not significantly different from that with halothane anesthesia, and no ST-segment deviation was observed in either group of patients. We assume, therefore, that $M\dot{V}o_2$ was appropriately decreased and that the optimum pressure range was maintained similarly by each agent, or that both of these were operative.

Our studies suggest (1) that HR did not change significantly following the induction of isoflurane or halothane anesthesia; (2) that, although cardiac output decreased significantly only after the induction of halothane anesthesia, we are unable to conclude that cardiac output was better maintained by isoflurane than halothane anesthesia—because of the small group of patients studied, the wide variation in cardiac output, and the higher cardiac output in the awake halothane group of patients; (3) that $\overline{AP}$ decreases similarly during both isoflurane and halothane anesthesia and, in this regard, neither agent is clearly superior for patients with coronary artery disease.

ACKNOWLEDGMENT

The assistance of Drs. J. R. Pluth and D. A. Barnhorst, Department of Surgery and Dr. W. F. Taylor, Medical Statistics in this study is gratefully acknowledged.

REFERENCES

1. Joas TA, Stevens WC: Comparison of the arrhythmic doses of epinephrine during Forane, halothane, and fluroxene anesthesia in dogs. Anesthesiology 35:48-53, 1971

2. Mazze RI, Cousins MJ, and Barr GA: Renal effects and metabolism of isoflurane in man. Anesthesiology 40:536-542, 1974

3. Cromwell TH, Eger EI II, Stevens WC, et al: Forane uptake, excretion, and blood solubility in man. Anesthesiology 35:401-408, 1971

4. Stevens WC, Cromwell TH, Halsey MJ, et al: The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. Anesthesiology 35: 8-16, 1971

5. Saidman LJ, Eger EI II, Munson ES, et al: Minimum alveolar concentrations of methoxyflurane, halothane, ether and cyclopropane in man: correlation with theories of anesthesia. Anesthesiology 28: 994-1002, 1967

6. Robertson JT, Schick RW, Morgan F, et al: Accurate placement of ventriculo-atrial shunt for hydrocephalus under electrocardiographic control. J Neurosurg 18:255-257, 1961

7. Seldinger SI: Catheter replacement of the needle in percutaneous arteriography: a new technique. Acta Radiol [Diagn] (Stockh) 39:368-376, 1953

8. Theye RA, Rehder K, Quesada RS, et al: Measurement of cardiac output by an indicator-dilution method. Anesthesiology 25:71-74, 1964

9. Rehder K, Forbes J, Alter H, et al: Halothane biotransformation in man: a quantitative study. Anesthesiology 28:711-715, 1967

10. Rehder K, Mallow JE, Fibuch EE, et al: Effects of isoflurane anesthesia and muscle paralysis on respiratory mechanics in normal man. Anesthesiology 41:477-485, 1974

11. Sharma GVRK, Kumar R, Molokhia F, et al: "Coronary steal": regional myocardial blood flow studies during isoproterenol infusion (Is) in acute and healing myocardial infarction (MI) (abstract). Clin Res 19:339, 1971

12. Gunnar RM, Loeb HS: Use of drugs in cardiogenic shock due to acute myocardial infarction. Circulation 45:1111-1124, 1972

13. Maroko PR, Braunwald E: Modification of myocardial infarction size after coronary occlusion. Ann Intern Med 79:720-733, 1973

Editors share the belief that medical writing is capable of vast improvement. This article is one of a series of personal communications from Charles G. Roland, M.D., former Senior Editor of JAMA, to John T. Martin, M.D., Associate Editor of Anesthesia & Analgesia . . . Current Researches. Dr. Roland is Chairman, Department of Biomedical Communications, Mayo Clinic, Rochester, Minnesota 55901.

Thoughts About Medical Writing

XXXIII. Parallelism is a Virtue

Dear Tom:

In interpreting the written word, the brain can sort through remarkable jumbles. It *can*. But the brain works more efficiently—i.e., understands more quickly and more completely—when thoughts are expressed clearly. One powerful tool that helps the writer to communicate clearly is parallelism.

I would define parallelism in writing as that condition in which entities that complement each other are verbalized in such a way that their relationship is properly emphasized. That abstract definition may itself defy understanding, so let me give some concrete examples.

This sentence was part of a recent journal article: "The special clamp and other methods have been used." What's wrong here? The reader must, after reading "other methods," go back to "clamp" and satisfy himself that the author probably has been merely careless in saying that a clamp is a method. Obviously, a clamp is a concrete thing, whereas methods are abstractions. Careful readers, readers who are striving to understand, probably make computations like this in nanoseconds and don't realize they are making them. But the brain must make an unnecessary reversal nonetheless. In this case, the author would have saved the step by writing: "The special clamp and other instruments have been used." The clamp is an instrument. The appropriate parallelism has been introduced.

Longer passages that contain words or phrases that should be parallel (but are not) force the reader's brain into much more complicated but impromptu efforts at revision. Often these longer instances of nonparallelism are the ones that will bubble into consciousness as the reader stops and thinks, "He really lost me there." Here's an example.

> Chest-wall stethoscopes, particularly the weighted models now available, are suitable monitors for patients who are awake, during induction or with mask-administered anesthetics.

Confusion indeed! Are the patients awake during induction of anesthesia? For whom are these stethoscopes suitable monitors? The writer of this sentence has devised an ingeniously nonparallel way of presenting his facts. Actually, once we've wrestled this information into submission it becomes obvious that three groups of patients are referred to—awake patients, patients having anesthesia induced, and patients having anesthetic gases given via a mask. But it takes a little mental computation to be sure. The author should have written something like this:

> Chest-wall stethoscopes, particularly the weighted models now available, are suitable monitors for patients who are awake, are having anesthesia in-

duced, or are having anesthetics administered via a mask.

That sentence contains proper parallelism. The published version was potentially confusing, which is a serious fault itself. But nonparallelism can be actually misleading. Consider this advice for patients:

General measures, such as rest, temperate habits, avoidance of activity, and the use of alcoholic beverages, should not be forgotten.

The literal, grammatical (but not necessarily correct) meaning of this sentence is clarified by numbering the measures that are listed after the "such as" phrase:

General measures, such as (1) rest, (2) temperate habits, (3) avoidance of activity, and (4) the use of alcoholic beverages, should not be forgotten.

Plainly, although the author cautions patients to have temperate habits, he also advises them to use alcoholic beverages. Is this what he really means? Of course not. But haste and carelessness have led him to publish an ambiguous recommendation. Probably be meant "avoidance of" to encompass both "activity" and "the use of alcoholic beverages." But that isn't what he wrote. He should have written something like this:

General measures should not be forgotten—e.g., rest and adoption of temperate habits, together with avoidance of activity and of alcoholic beverages.

This revision logically pairs the things a patient should do and then pairs the things he shouldn't do. The message is clear and unequivocal.

Some English constructions require parallelism. These constructions are linked comparisons using correlative conjunctions such as "both . . . and," "either . . . or," and "not only . . . but also." I think that "either . . . or" is the most abused of these couplets. This next sentence exemplifies the nonparallelism that often arises:

The Mycoplasmas were identified either by their ability to split urea or typical colonial morphology as shown on buffered agar.

As written, the sentence grates on a reader's mind. He might logically expect the Mycoplasmas' ability to split urea to be followed by a description of their ability to split something else. There is a rule that should be applied: Express parallel ideas in the same grammatical form; whatever part of speech follows *either* should also follow *or*. If the author had followed this rule, the sentence would have been clearer. In this case, parallelism would have been furthered by adding a second preposition (*by*) and "their," as in this revision:

The Mycoplasmas were identified either by their ability to split urea or by their typical colonial morphology as shown on buffered agar.

The human mind is adept at listing and at comparing. When an author omits parallelism, the brain must work needlessly to provide what the author did not. Let's save brainpower for the necessary jobs.

Regards,

[Charles G. Roland, M.D.]

LACTIC ACIDOSIS Idiopathic lactic acidosis may arise from excessive production of lactic acid in any tissue or from an inability of the liver to metabolize lactate. A case is described in which sodium nitroprusside administered to a patient with congestive heart failure and idiopathic lactic acidosis had the unexpected effect of improving the acidemia (pH rising from 7.19 to 7.61). It was speculated that vasodilation caused redistribution of the cardiac output (possibly increasing hepatic blood flow) such that lactic acid metabolism was restored. *(Taradash MR, Jacobson LB: Vasodilation therapy of idiopathic lactic acidosis. NEJM 293:468-471, 1975)*

Case History Number 88: Gas Embolism During Encephalography

WILLIAM L. PAUL, MD
EDWIN S. MUNSON, MD

Patient #1.—A 14-year-old male was admitted to the hospital with a two-week history of intermittent headache, vertigo, anorexia, nausea and vomiting. Three years previously a suboccipital craniotomy had been performed for removal of a pineal teratoma and placement of a ventriculoperitoneal shunt. Physical examination on the present admission was unremarkable except that the ventriculoperitoneal shunt did not appear to be functioning properly. The neurosurgeons thought that the shunt was nonfunctional, that some degree of hydrocephalus was present, and the patient was scheduled for pneumoencephalography. Preoperatively, he received pentobarbital 100 mg, atropine 0.4 mg IM, and on arrival in the x-ray department he appeared sedated. A catheter was placed in a forearm vein for the administration of small doses of Innovar. After the patient was in the pneumoencephalographic chair, a ventriculostomy was performed. A pressure transducer was attached to the ventriculostomy catheter which showed the opening pressure to be 2 torr. Oxygen was used as the contrast gas medium. After several exchanges of cerebral spinal fluid for gas, a total of 50 ml oxygen was injected into the ventricular space. At this time the patient became restless and 50 percent nitrous oxide inhalation was administered by mask. Ventriculograms revealed that the ventricles were not well outlined and contained only a small amount of contrast medium. It was also noted that the CSF pressure remained at 2 torr. An explanation for these findings became apparent when it was noted on the ventriculogram (fig 1) that gas was present within the ventricular shunt tubing. It was concluded that the ventriculoperitoneal shunt was functional and that no hydrocephalus nor obstruction to ventricular fluid dynamics was present. The procedure was concluded and the patient made a satisfactory recovery. Three months later the patient died and at autopsy a hypothalamic tumor was found.

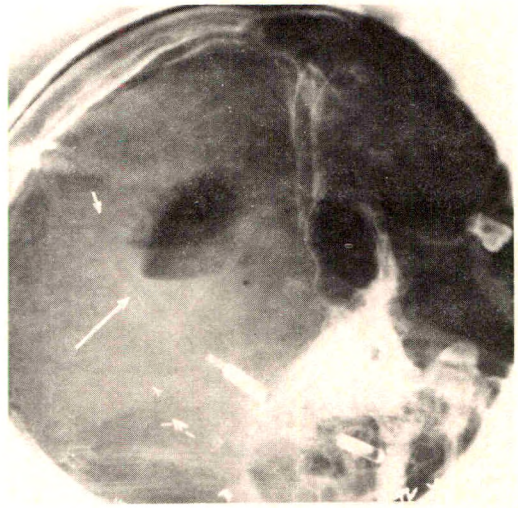


FIG 1. A ventriculogram with the patient in the brow-up position shows the contrast gas (oxygen) in the anterior horns of the lateral ventricles. Note the presence of gas within the shunt catheter (long arrow). The catheter tip is identified by the short arrow. The body of the shunt apparatus and surgical clips from a previous operation also are visible.

From the Department of Anesthesiology, University of Florida College of Medicine, Box J254, J. Hillis Miller Health Center, Gainesville, Florida 32610.

This manuscript was supported in part by a grant from the United States Public Health Service, Grant #GM00427-12.

This feature is conducted by Edwin S. Munson, M.D., Department of Anesthesiology, University of Florida College of Medicine, Gainesville, Florida 32610.

Patient #2.—A 6-year-old female was admitted to the hospital with a three-day history of intermittent headache and decreased appetite. At four months of age she was found to have severe communicating hydrocephalus and underwent placement of a ventriculoatrial shunt. The shunt functioned normally until the present admission when hydrocephalus secondary to a non-functional shunt mechanism was diagnosed. Hematologic and blood chemistries were within normal limits.

The patient was scheduled for ventriculography. Preoperatively she received pentobarbital 65 mg, meperidine 20 mg, and atropine 0.3 mg IM and she was well sedated on arrival for the procedure. After she was placed in the pneumoencephalography tilt chair, catheters were positioned in peripheral and central veins. Anesthesia was induced with 75 mg thiopental IV and intubation was facilitated by 40 mg succinylcholine. Anesthesia was maintained with halothane, one percent in combination with nitrous oxide in 50 percent concentration. An esophageal stethoscope was used to monitor heart sounds.

Because of the experience with the ventricular shunt in the previous patient, it was elected to use nitrous oxide as the contrast gas medium. Approximately 15 ml of nitrous oxide were injected in divided doses into the shunt reservoir. To distribute the gas within the ventricular system, the patient was rotated 360° in the saggital plane, as if performing a forward somersault. When the patient returned to the original supine position, a harsh high-pitched systolic murmur was heard. No change in pulse rate or arterial blood pressure occurred. Nitrous oxide was immediately discontinued from the inspired gas and the lungs were ventilated with 100% oxygen. The cardiac murmur gradually disappeared over the next five minutes. Repeated attempts to aspirate blood through the central venous catheter were unsuccessful. After an additional five-minute period, when normal heart sounds had returned, nitrous oxide inhalation was reinstituted. Almost immediately the cardiac murmur returned. Nitrous oxide was discontinued and the procedure terminated. The ventriculogram showed the tip of the ventricular catheter to be within the anterior horn of the right lateral ventricle.

The patient was placed in the left lateral decubitus position and oxygen was administered through the endotracheal tube. Thirty minutes later, analysis of arterial blood gases showed oxygenation and ventilation to be normal. Chest x-rays at this time were also normal. An hour later the endotracheal tube was removed and the patient recovered without incident.

DISCUSSION

With the development of ventriculoatrial and ventriculoperitoneal shunts to control CSF pressure and hydrocephalus, anesthesiologists often are involved with the management of these patients during pneumoencephalography. Frequently, as presented in Case History #1, the evaluation involved determining shunt patency. A crude clinical assessment of shunt function is usually made by depressing the shunt reservoir. If the reservoir fills in less than one minute the volume of ventricular CSF may be normal or elevated. If the ventricles are collapsed as a result of decreased CSF pressure, or from shunt malfunction, the reservoir will not fill.

This case shows another method for determining shunt patency which has not previously been reported, namely, the failure of CSF pressure to rise following inhalation of nitrous oxide when air or oxygen is used as contrast gas media. The hazard of rapid and severe increases in CSF pressure during air encephalography during nitrous oxide anesthesia has been described by Saidman and Eger.[1] This mechanism results from the greater solubility of nitrous oxide in blood compared with nitrogen. The differential solubility between nitrous oxide and oxygen (about 1:6) also should result in an increase in CSF pressure, but to a lesser extent than with air. This patient (#1) did not exhibit any increase in CSF pressure, probably the result of the functioning shunt. Had a ventriculoatrial shunt been present venous embolism undoubtedly would have occurred as observed in patient #2.

Venous air embolism has long been recognized as a complication of pneumoencephalography.[2] The events described with patient #2 and the recent report of Youngberg et al[3] illustrate this potential hazard in patients with ventriculoatrial shunts. In this regard, the selection of the contrast medium (air, oxygen, or nitrous oxide) is important. During inhalation of nitrous oxide, no increase in CSF pressure results when the contrast gas also is nitrous oxide.[4] This technic appears to offer maximal safety in preventing a rise in CSF pressure.

However, should venous embolization of nitrous oxide occur, the embolized bubbles would tend to be held in the gas phase due to the high partial pressure of the anesthetic in venous blood. Thus, embolized nitrous oxide would be rendered "insoluble" in venous blood until pulmonary excretions of nitrous oxide occurred. When discontinued from inspired gases, nitrous oxide is rapidly eliminated from the lung, blood and cerebral ventricles. Furthermore, relatively rapid absorption of intraventricular nitrous oxide would prevent the occurence of delayed gas embolism.[5] When oxygen is used as the contrast gas medium, some rise in CSF pressure may occur, but the low partial pressure of oxygen in venous blood would tend to maintain a relatively greater solubility thus promoting gas absorption which would not be affected by the presence of nitrous oxide. However, since oxygen may linger in the cerebral ventricles for as long as 24 hours following encephalography[6] the patient would have to be carefully observed in the postanesthetic period.

Youngberg et al[3] have suggested that venous air embolism during encephalography can be avoided or minimized in patients with ventriculoatrial catheters by: 1) attempting to keep the air fluid level above the tip of the shunt catheter; 2) avoiding air as a contrast medium; 3) using a central venous catheter for gas aspiration; 4) continuously monitoring ECG; 5) using the Doppler flow probe monitor over the right heart; and whenever possible, 6) ligating or clamping the shunt catheter prior to encephalography.

Additional monitors which would facilitate early detection of venous air embolism also include end-tidal CO_2 monitoring during constant volume ventilation and the use of a Swan-Ganz catheter for continuous measurement of right ventricular or pulmonary artery pressures.[7] Should venous air embolism occur, the treatment is symptomatic and directed toward preventing further air entry and restoring normal cardiopulmonary function. Placement of the patient in the left lateral decubitus position is advantageous because the apex of the heart is placed above the level of the pulmonic

Comment

ROBERT K. STOELTING, M.D.

Gas encephalography requiring inhalation anesthesia may produce changes that require an understanding of differential gas solubility. For example, increased intracranial pressure during N_2O inhalation and air or oxygen injection into the cerebral ventricles occurs because of the greater solubility of nitrous oxide as compared with nitrogen. The present report describes a possible diagnostic use of N_2O inhalation to determine patency of a ventriculoperitoneal shunt and emphasizes the hazards of venous air embolism and the rationale for the contrast and anesthetic gases chosen in the presence of a functional ventriculoatrial shunt.

An additional consideration when using N_2O as the contrast gas is its rapid disappearance from the ventricles when N_2O inhalation is discontinued. This has resulted in rapid reduction of CSF pressure and subsequent cardiovascular collapse.[1]

A method providing similar information as gas encephalography but not requiring a contrast gas would be useful. Computer-assisted transverse axial tomography (EMI scanner) permits such an examination. Furthermore, sedation is necessary only for the uncooperative patient. It is unlikely that this radiologic technic will completely eliminate the need for gas encephalography but the frequency will surely be reduced. Indeed, in a recent report, the number of gas encephalograms decreased 60 percent following the introduction of the EMI scanner.[2]

REFERENCES

1. Collan R, Iivanainen M: Cardiac arrest caused by rapid elimination of nitrous oxide from cerebral ventricles after encephalography. Can Anaes Soc J 16:519-524, 1969

2. Baker HL, Houser W, Campbell K et al: Computerized tomography of the head. JAMA 233:1304-1308, 1975

valve, thus promoting relief of right ventricular outflow obstruction and clearance of intracardiac gas.[8] The pneumoencephalography tilt chair facilitates placing the patient in this position. Elimination of nitrous oxide from the lung will reverse the bubble amplification effect on intrapulmonic bubbles[9] and an increased F_{IO_2} will tend to overcome the hypoxemia caused by intrapulmonary shunting. The use of vasopressors and closed-chest cardiac massage also have been advocated for the treatment of profound arterial hypotension and cardiac arrest.[10]

REFERENCES

1. Saidman LJ, Eger EI II: Change in cerebrospinal fluid pressure during pneumoencephalography under nitrous oxide anesthesia. Anesthesiology 26: 67-72, 1965

2. King AB, Otenasek FJ: Air embolism occurring during encephalography. Report of two cases. J Neurosurg 5:577-579, 1948

3. Youngberg JA, Kaplan JA, Miller ED: Air embolism through a ventriculoatrial shunt during pneumoencephalography. Anesthesiology 42:487-490, 1975.

4. Saidman LJ: Complications related to anesthetic solubility, In Complications of Anesthesia. Edited by LJ Saidman and F Moya. Springfield, Charles C Thomas, 1970, pp 21-26

5. Heppner F: Air embolism eight hours after ventriculography. Acta Radiologica 38:294-298, 1952

6. Aird RB: Experimental encephalography with anesthetic gases. Arch Surg 32:193-217, 1936

7. Munson ES, Paul WL, Perry JC, et al: Early detection of venous air embolism using a Swan-Ganz catheter. Anesthesiology 42:223-226, 1975

8. Durant TM, Long J, Oppenheimer MJ: Pulmonary (venous) air embolism. Am Heart J 33:269-281, 1947

9. Munson ES: Effect of nitrous oxide on the pulmonary circulation during venous air embolism. Anesth & Analg 50:785-793, 1971

10. Ericsson JA, Gottlieb JD, Sweet RB: Closed-chest cardiac massage in the treatment of venous air embolism. N Engl J Med 270:1353-1354, 1964

Comment

JOHN A. YOUNGBERG, M.D.,
Major, MC
Department of Anesthesia
Brooke Army Medical Center
Fort Sam Houston, Texas 78234

The two cases present possible complications of central nervous system diagnostic procedures performed when patent ventriculoperitoneal or ventriculoatrial shunts are present. They demonstrate why patients with such shunts should be carefully monitored and why an anesthesiologist should be in attendance.

Case #1 demonstrates the embolization of the contrast gas through the shunt to the peritoneal cavity. This apparently resulted in no injury to the patient and showed the patency of the shunt.

Case #2 is more interesting. We previously have described embolization through a patent ventriculoatrial shunt and its possible sequelae.[1] Approximately 90% of patients with gas emboli develop murmurs; 65% develop arrhythmias, and 68% have hypotension.[2] The authors report the presence of a "harsh, high-pitched systolic murmur" in this patient, but do not report the occurrence of hypotension or an arrhythmia. The central venous catheter apparently was not functional precluding confirmation of diagnosis by aspiration of gas. Without measuring aspiration of gas from the heart, the diagnosis of gas embolization is tenuous unless there is a sudden onset of a murmur accompanied by a significant alteration in cardiac rhythm or arterial blood pressure.[2]

An attempt was made to duplicate events in this case in a dog model.† A 20.4 kg mongrel dog was anesthetized with 1% halothane and 50% nitrous oxide in oxygen. Respirations were controlled. A central venous catheter was placed in the right external jugular vein, attached to a strain gauge, and advanced until a right atrial wave form was obtained. A Doppler chest probe was positioned over the heart. A 7 ml (0.3 ml/kg) bolus of nitrous oxide was administered through the central venous catheter. A harsh, systolic murmur was heard almost instantly and the animal was ventilated with oxygen. During the time the murmur was audible, there was a marked drop in pulse pressure but no change in pulse rate or any audible change in cardiac rhythm. After 2.5 minutes, the murmur was no longer audible. Ventilation with oxygen was continued for an additional five minutes when 1% halothane and 50% nitrous oxide in oxygen was reinstituted. There was no recurrence of any cardiac murmurs.

This experiment raises questions as to

*The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

†Appreciation is expressed to Gary Welch, M.D., Brian Ribak, M.D., and Mr. Walker in performing the animal experiment.

the etiology of the recurrence of the murmur described in Case #2. Nitrous oxide embolization could have been continued through the shunt to the heart, or a quantity of air may have inadvertently been injected into the ventricular system together with the nitrous oxide, thus producing nitrous oxide-air embolization. In this latter case, when nitrous oxide inhalation was discontinued, the size of the bubble would decrease secondary to absorption of nitrous oxide into the blood and loss of the murmur, but would again increase in size when nitrous oxide inhalation was instituted. However, in this patient, the time sequence makes this possibility unlikely.

The patency of a ventriculoatrial shunt may be evaluated by employing a contrast material such as meglumine iothalamate 60%, prior to performing diagnostic procedures. However, potential hazards of seizure activity or arachnoiditis exist with such agents.[3,4] In the presence of a patent shunt, it may be more advantageous to utilize meglumine iothalamate 60%, or carbon dioxide, to perform such studies.[1]

REFERENCES

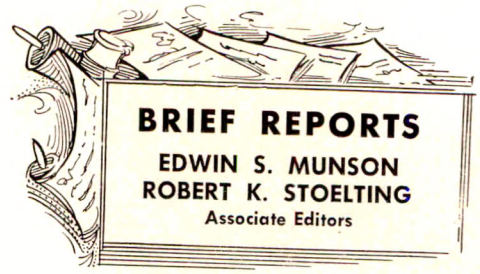
1. Youngberg JA, Kaplan JA, Miller ED: Air embolism through a ventriculoatrial shunt during pneumoencephalography. Anesthesiology 42:487-490, 1975

2. Michenfelder JD, Martin JT, Alfenberg BM, et al: Air embolism during neurosurgery. JAMA 208:1353-1358, 1969

3. Cornejo SG: Conroy ventriculography in the diagnosis of intraventricular and posterior fossa lesions. J Neurosurg 34:405-407, 1971

4. Weiss SR, Raskin R: Conroy ventriculography in the diagnosis of brain tumors and congenital malformations in children. J Neurosurg 34:408-411, 1971

INTRAVENOUS FLUIDS An intravenous solution that could reduce protein wasting and be administered through peripheral veins would be useful postoperatively until an adequate oral intake could be established. The metabolic effects of a 3 per cent amino acid solution vs a 5 per cent dextrose solution were compared during the first 6 postoperative days after head and neck or abdominal operations. Nitrogen losses for patients receiving the amino acid solutions were significantly less than for patients receiving 5 per cent dextrose. Phlebitis occurred with equal frequency in both groups. The speculated mechanism for nitrogen sparing was decreased serum glucose and insulin levels allowing greater fat mobilization and utilization with subsequent sparing of lean body mass. *(Hoover HC, Grant JP, Gorschboth C et al: Nitrogen-sparing intravenous fluids in postoperative patients NEJM 293:172-175, 1975)*



Fire Hazard During CO_2 Laser Microsurgery on the Larynx and Trachea

JOHN C. SNOW, MD*
MARTIN L. NORTON, MD†
TEJINDER S. SALUJA, MD‡
ADORACION F. ESTANISLAO, MD§
Boston, Massachusetts‖

In a previous report,[1] we described the use of the CO_2 laser for microsurgery on the larynx and trachea in 392 procedures under general endotracheal anesthesia. No morbidity or mortality was found related to this technic. We have now performed a total of 700 such procedures on 250 patients over a 42-month period (1972-1975). No side effects related to the procedure had been seen, nor had there been any injuries to patients or operating room personnel. However, within the last 6 months, 4 patients sustained burns of the tracheal mucosa from the impact of the laser beam on the endotracheal tube. In all 4 cases, the fire was extinguished promptly and the burns healed uneventfully. Two of the cases will be described in detail.

REPORT OF CASES

Case 1.—A 12-month-old girl was admitted to the hospital with a tracheotomy since the age of 3 months and recurrent laryngeal papillomas which produced complete obstruction of the larynx. The following day, induction and maintenance of anesthesia were accomplished with nonflammable anesthetics, and an uncuffed red-rubber Rusch endotracheal tube was inserted through the tracheotomy. The tube was not wrapped with aluminum tape. The larynx was exposed with a pediatric laryngoscope and placed on the suspension apparatus. A Zeiss operating microscope with laser attachment was brought into position.

When the laser beam was continuously

*Professor of Anesthesiology.
†Associate Professor of Anesthesiology.
‡Resident in Anesthesiology.
§Resident in Anesthesiology.
‖Department of Anesthesiology, Boston University School of Medicine and University Hospital, Boston, Massachusetts 02118.

Paper received: 6/16/75
Accepted for publication: 7/5/75

discharged, the papillomas obstructing the larynx were vaporized, so that the laser beam impacted on the tube within the trachea at the tracheotomy level. A fire started, which was brought under control immediately, by removal of the burning tube. Examination of the endotracheal tube revealed a superficial burned area, 1 x 0.5 cm in size, 4 cm from the distal end. Bronchoscopy revealed a small superficial burn of the tracheal mucosa, which later healed.

Case 2.—A 12-year-old boy was anesthetized with nonflammable anesthetics for CO_2 laser microsurgery of recurrent laryngeal papillomas. An uncuffed red-rubber Rusch oral endotracheal tube was used and was protected with aluminum foil except for the distal 1.5 cm of the tube. During the operation, the laser beam repeatedly hit the unprotected distal end of the tube. A fire started, which was brought under control immediately by removal of the burning tube. Examination of the tube showed a superficial burned area, 1.2 x 0.5 cm in size, including the aperture opposite the beveled end of the endotracheal tube. Bronchoscopy revealed a small superficial burn of the tracheal mucosa, 1 cm below the vocal cords, which healed uneventfully.

DISCUSSION AND SAFETY PRECAUTION RECOMMENDATIONS

The wavelength of the CO_2 laser beam is in the infrared range (10.6 microns), so the destructive capacity of the beam is limited to a thermal effect. The heat produced may ignite unprotected anesthesia equipment or flammable anesthetic agents. Plastic and rubber equipment, such as endotracheal tubes, oropharyngeal airways, nasogastric tubes, and esophageal stethoscopes, easily can be set on fire by a misdirected laser beam.

During CO_2 laser microsurgery on the larynx and trachea, we have observed that if the laser beam repeatedly hits the red-rubber Rusch endotracheal tube (4 or 5 times) in the same area, there is the risk of fire. The laser beam must be carefully focused to avoid impact with the tube.

If a patient has a tracheotomy, anesthesia can be administered either through a metal tracheotomy tube or a Rusch red-rubber endotracheal tube. However, if the red-rubber endotracheal tube is situated within the operative field, it must be protected with a reflective surface in order to avoid laser beam damage and fire. A thin metal coating, such as self-adhesive aluminum tape, placed around the distal portion of the tube, not including the cuff, will protect the tube from accidental laser impact. The cuff cannot be protected without limiting its function.

Fewer safety precautions are necessary with CO_2 laser than with ruby, argon or other lasers. The operating room personnel need only to wear ordinary eyeglasses to protect their corneas from injury should the laser beam accidentally be reflected from a metal surface. For the same reason, the patient's eyes also must be taped shut. If an area of tissue close to the target area needs to be protected, it can be shielded adequately by moist gauze, since water dissipates the energy effectively. Pregnant personnel are not at risk. The laser beam is not like an x-ray, in that its effects are limited to accessible areas.

All nonflammable inhalation anesthetic agents can be administered to patients undergoing laser surgical procedures.[2] The potential electrical and explosive hazards associated with the use of the laser are no greater than those with the use of high-frequency electrosurgery.[3]

REFERENCES

1. Snow JC, Kripke BJ, Strong MS, et al: Anesthesia for carbon dioxide laser microsurgery on the larynx and trachea. Anesth & Analg 53:507-512, 1974

2. Birch AA: Anesthetic considerations during laser surgery. Anesth & Analg 52:53-58, 1973

3. Goldman L, Rockwell RJ, Fidler JP, et al: Investigative laser surgery: safety aspects. Biomed Eng 4:415-418, 1969

A New Introducer for Percutaneous Cardiovascular Catheters

JOHN M. GOODING, DO*
GUENTER CORSSEN, MD†
Birmingham, Alabama‡

SINCE its introduction, the Swan-Ganz catheter has been effective for evaluation of myocardial performance. Because of the seemingly complicated technic of inserting the catheter, as originally described by the authors,[1] many clinicians still prefer the placement of central venous pressure lines. The recent development of an introducer§ has made central venous sites more accessible for pulmonary artery catheterization. The introducer consists of a 17-gauge needle covered by an inner and outer plastic sheath (figure). The special design of the introducer makes possible the percutaneous puncture of the internal jugular or subclavian vein, as described elsewhere.[2-4]

The basic technic of catheterization involves the following steps:

1. Surgical preparation with antimicrobial solution and appropriate draping.

2. Local infiltration of the site of vein puncture with a suitable local anesthetic.

3. Small stab wound through the skin and subcutaneous tissue with a #11 scalpel blade.

4. Advancement of the introducer, to which a 10 ml syringe is attached, into a central vein, and aspiration of venous blood.

§Percutaneous Cardiovascular Catheter Introducer, Edwards Laboratories, Santa Ana, California.

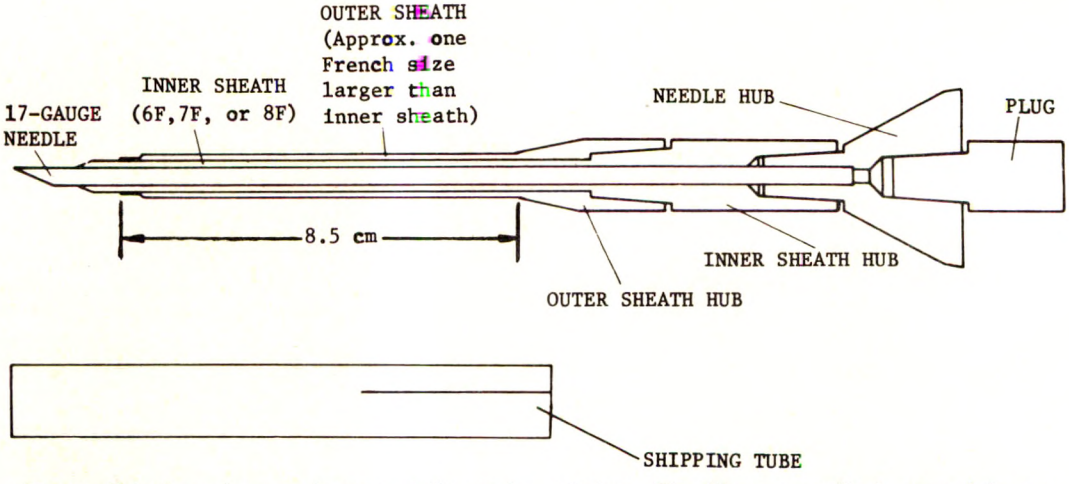


FIGURE. Introducer for percutaneous cardiovascular catheters. The 17-gauge needle is covered by an inner and outer plastic sheath.

*Assistant Professor.

†Professor and Chairman, Department of Anesthesiology.

‡Department of Anesthesiology, The University of Alabama School of Medicine, Birmingham, Alabama 35294.

Paper received: 6/2/75
Accepted for publication: 8/25/75

5. Upon successful venous aspiration, the introducer is advanced (approximately 0.5 cm) to ensure intravascular placement of the needle bevel as well as the distal tips of the inner and outer plastic sheaths.

6. The needle is withdrawn and the inner and outer sheaths are advanced simultaneously.

7. The hub plug is attached to the hub of the inner sheath to prevent excessive venous backflow in high venous pressure states and air embolization in low venous pressure states.

8. When catheterization is about to begin, the inner sheath is withdrawn, holding the outer sheath in place, and the catheter is rapidly introduced through the outer sheath.

9. Once the catheter is advanced to 10 cm within the vein, the outer sheath can be removed from its intravenous site and drawn snug proximally on the catheter, where it is held in place.

It is preferable to inflate the balloon when the catheter is approximately 10 to 12 cm within the vein. The catheter is then connected to a pressure transducer and the pressure wave is recorded either on an oscilloscope or write-out recorder. While advancing the catheter, the location of its tip is determined by observing the changes in the contour of the pressure wave.

DISCUSSION

Originally, the pulmonary artery catheter was inserted via an antecubital vein cutdown.[1] It has been our experience that this approach is frequently unsuccessful, due to site inaccessibility or failure in traversing the shoulder veins. The antecubital cutdown approach is also time consuming. If the catheter is not passed to the pulmonary artery within a reasonable time after initial insertion from the antecubital fossa, the catheter is warmed by body temperature and becomes pliable, leading to possible looping or knotting and to difficulty in advancing.

With access through a central vein, pulmonary artery catheterization can be rapid, simple, and does not require a cutdown. The technic has a higher incidence of success, can be used when peripheral sites are not accessible, and follows a more direct route to the right heart than the peripheral approach. There seems also to be a lesser incidence of thrombophlebitis.

To date, we have completed 82 catheterizations with the percutaneous cardiovascular introducer. The only reportable complication has been one incidence of pneumothorax in a patient with clavicular anatomic abnormality due to an old fracture. Minor oozing may occur around the puncture site; however, this may be effectively controlled with adequate local compression. We have had no other complications related to use of the introducer.

REFERENCES

1. Swan HJC, Ganz W, Forrester J, et al: Catheterization of the heart in man with the use of a flow-directed balloon-tipped catheter. N Engl J Med 283:447-451, 1970

2. Daily PO, Griepp RB, Shumway NE: Percutaneous internal jugular vein cannulation. Arch Surg 101:534-536, 1970

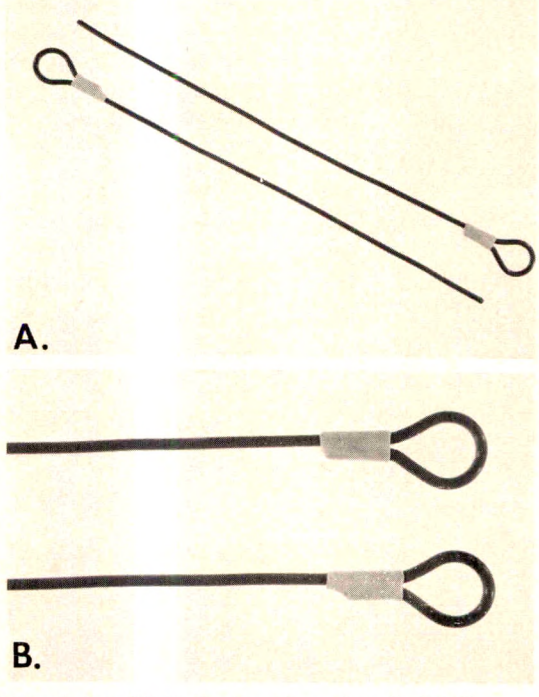
3. Corwin JH, Mosely T: Subclavian venipuncture and central venous pressure, technique and application. Am Surg 32:413-415, 1966

4. Yoffa D: Supraclavicular subclavian venipuncture and catheterisation. Lancet 2:614-617, 1975

Plastic Covered Solid Copper Wire Stylet

MORRIS J. NICHOLSON, MD
Boston, Massachusetts*

AN EFFECTIVE and inexpensive flexible stylet can be made from commercially available #12 TW (thermoplastic weatherproof) copper wire (figure, A). The proximal looped end can be held tight by using a 9-mm heat-shrinkable plastic tube (figure, B). Sterilization is by soaking in alcohol, autoclaving, or exposure to ethylene oxide. The distal end of the plastic end of the plastic tubing covering the copper wire can be heat sealed.



*Department of Anesthesiology Lahey Clinic, Boston, Massachusetts 02115.

Paper received: 2/28/75
Accepted for publication: 5/9/75

International Anesthesia Research Society

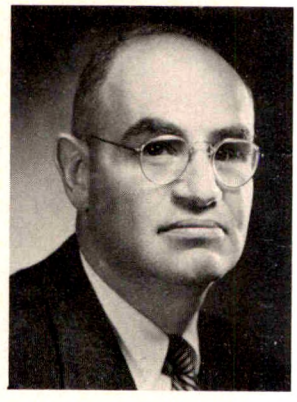
50th congress

An Important Milestone for
Anesthesiology's Pioneer Organization

March 14–18, 1976
Caesars Palace
Las Vegas, Nevada

Program

Eleventh Annual Becton, Dickinson and Company Oscar Schwidetzky Memorial Lecture



TUESDAY, MARCH 16 - 2 P.M.

"ON THE HISTORY OF IDEAS IN ANAESTHESIA"

Leroy David Vandam, M.D.
Professor of Anaesthesia,
Harvard Medical School;
Anesthesiologist-in-Chief,
Peter Bent Brigham Hospital,
Boston, Massachusetts

Golden Anniversary Commemorative Luncheon

Tuesday, March 16 - 12 p. m.

T. H. Seldon, M.D., Chairman, 50th Congress Program Committee; Editor, ANESTHESIA and ANALGESIA . . . Current Researches.

John W. Ditzler, M.D., President, American Society of Anesthesiologists.

John H. A. Lawrence, M.D., President, Canadian Anaesthetists' Society.

The Fourteenth Annual Baxter-Travenol Lecture

WEDNESDAY, MARCH 17 - 2 P.M.

"EPIDEMIOLOGICAL ANSWERS TO LABORATORY QUESTIONS IN ENVIRONMENTAL CANCER"

Irving J. Selikoff, M.D.
Professor of Medicine,
Professor of Community Medicine;
Director, Environmental Sciences
Laboratory, Mount Sinai School of
Medicine, New York, New York

Monday, March 15, 1976 - Scientific Program

Morning: *Chairman: Kenneth K. Keown, M.D., Columbia, Missouri,* Chairman of the Board of Trustees, I.A.R.S.

8:30 **A TOTALLY CLOSED ANESTHESIA SYSTEM THAT CONTINUOUSLY MEASURES O_2 CONSUMPTION AND N_2O UPTAKE**

Kenneth A. Haselby, M.D.

Discussor: Edmond I. Eger, II, M.D.

8:55 **MORE DEFINITE CONTROL OF BALANCED ANESTHESIA USING OXYGEN CONSUMPTION VARIATIONS**

*William S. Jordan, M.D.
Dwayne R. Westenskow, M.D.

Discussor: Kai Rehder, M.D.

9:20 **LYMPHOCYTE STUDIES IN POSTOPERATIVE PATIENTS**

*David L. Bruce, M.D.
Parviz Behbahani, M.D.
Paul C. Land, M.D.

Discussor: M. T. Jenkins, M.D.

9:45 **MECHANICAL VENTILATORY PATTERN, INTRAPLEURAL PRESSURE AND CARDIAC OUTPUT**

*John B. Downs, M.D.
Michael E. Douglas, Major, USAF, MC

Discussor: Douglas B. Craig, M.D.

10:10 — — — **INTERMISSION** — — —

11:00 **RESPIRATOR MANAGEMENT OF 1000 AND 2000 GRAM NEONATES—OUTCOME AND COMPLICATIONS**

John S. McDonald, M.D.

Discussor: Dean Crocker, M.D.

11:25 **A DOUBLE-BLIND EVALUATION OF THE EFFECTS OF KETAMINE ON NEUROBEHAVIORAL TESTS DURING THE FIRST TWO DAYS OF LIFE**

Robert Hodgkinson, M.D.
*Gertie F. Marx, M.D.
S. S. Kim, M.D.
Nora I. Miclat, M.D.

Discussor: Walter U. Brown, Jr., M.D.

*Will present paper.

Monday, March 15 - Scientific Program

Afternoon:
Room A

Chairman: Robert K. Stoelting, M.D., Indianapolis, Indiana, Member of Board of Trustees, I.A.R.S.

1:30 **EFFECT OF SODIUM NITROPRUSSIDE ADMINISTRATION ON REGIONAL BLOOD FLOW DISTRIBUTION**

*Ronald J. Gordon, Ph.D.
Gordon G. Dorris, M.S.
Jerry Collins, Ph.D.
Joseph Utley, M.D.
Mark B. Ravin, M.D.

Discussor: Ronald L. Katz, M.D.

1:55 **EFFECTS OF SODIUM NITROPRUSSIDE AND MEPHENTERMINE SULFATE ON RENAL BLOOD FLOW IN PATIENTS UNDERGOING NEPHROLITHOTOMY**

*Alexander A. Birch, M.D.
William H. Boyce, M.D.

Discussor: John D. Harries, M.D., F.R.C.P.(C)

2:20 **A DOSAGE NOMOGRAM FOR SODIUM NITROPRUSSIDE INDUCED HYPOTENSION UNDER ANESTHESIA**

*Noel W. Lawson, M.D.
Dola S. Thompson, M.D.
Carl L. Nelson, M.D.
Joan W. Flacke, M.D.
Edward R. Norton, M.D.

Discussor: Robert K. Stoelting, M.D.

2:45 — — — **INTERMISSION** — — —

3:15 **EFFECT OF HALOTHANE AND PENTOBARBITAL ANESTHESIA ON THE DISPERSION OF INDICATOR PARTICLES PASSING THROUGH THE CENTRAL CIRCULATION OF A DOG**

*Guy C. Davis, Jr., M.D., Ph.D.
A. William Paulsen, M.M. Sc.
Evan L. Frederickson, M.D.

Discussor: James B. Bassingthwaighte, M.D., Ph.D.

3:40 **HALOTHANE EFFECTS ON CONDUCTIVITY OF THE AV NODE**

John L. Atlee, III, M.D.

Discussor: Dean H. Morrow, M.D.

4:05 **EFFECT OF HALOTHANE ON SYSTOLIC TIME INTERVALS**

*Jan D. Hasbrouck, M.D.
Catherine C. Coleman, B.S., A.S.C.P.

Discussor: John A. Reitan, M.D.

4:30 **HEMODYNAMIC EFFECTS OF HALOTHANE IN DOGS RECEIVING PROPRANOLOL**

*Mark B. Ravin, M.D.
Alan Hymanson, B.S.
Joseph Utley, M.D.
Jerry Collins, Ph.D.

Discussor: David Shands, M.D., Ph.D.

*Will present paper.

Monday, March 15 - Scientific Program

Afternoon:
Room B

Chairman: Dean H. Morrow, M.D., Houston, Texas,
Contributing Editor, "Anesthesia and Analgesia"

1:30 **NEUTROPHIL CHEMOTAXIS DURING AND AFTER GENERAL ANESTHESIA**

*Theodore H. Stanley, M.D.
Gary E. Hill, M.D.
Harry Hill, M.D.

Discussor: David L. Bruce, M.D.

1:55 **CORRELATION OF PLASMA CHOLINESTERASE ACTIVITY AND DURATION OF ACTION OF SUCCINYLCHOLINE DURING PREGNANCY**

*Casey D. Blitt, M.D.
W. Clayton Petty, M.D.
Eva Alberternst, C.R.N.A.
Barbara J. Wright

Discussor: Oscar J. Viegas, M.D.

2:20 **A DUAL ACTION OF PANCURONIUM ON SUCCINYLCHOLINE NEUROMUSCULAR BLOCK**

*Anthony D. Ivankovich, M.D.
Naomi A. Sidell, M.D.
Ronald F. Albrecht, M.D.
A. Dietz, Ph.D.

Discussors: John W. R. McIntyre, M.D.
Anis Baraka, M.D.

2:45 — — — **INTERMISSION** — — —

3:15 **EVALUATION OF MONITORED RELAXANT DOSAGE AND RECOVERY CRITERIA BY PROGRAMMED TWITCH-TETANUS AND TRAIN-OF-FOUR ULNAR-NERVE STIMULATION**

*James O. Elam, M.D.
Mohamad Shafieha, M.D.
Phebe Lim Tan, M.D.
Jonathan Wooster, E.E.

Discussor: Hassan H. Ali, M.D.

3:40 **NEUROMUSCULAR BLOCK BY ANTIBIOTICS: POLYMYXIN B**

*Chingmuh Lee, M.D.
Dennis Hui-Ting Chen, M.D.
Eugene L. Nagel, M.D.

Discussor: Ronald D. Miller, M.D.

4:05 **RENAL FAILURE AND DURATION OF ACTION OF NEOSTIGMINE AND PYRIDOSTIGMINE**

*Ronald D. Miller, M.D.
Laura L. Roderick, A.B.
Lawrence D. Becker, M.D.

Discussor: Leonard F. Walts, M.D.

4:30 **HEMODYNAMIC EFFECTS OF METOCURINE IN PATIENTS WITH CORONARY ARTERY DISEASE AND BETA BLOCKADE**

*Daniel M. Philbin, M.D.
James Zaiden, M.D.
Robert P. Antonio, M.D.
John J. Savarese, M.D.

Discussor: Richard P. Fogdall, M.D.

*Will present paper.

Tuesday, March 16 - Scientific Program

Morning:
Room A

Chairman: David E. Longnecker, M.D., Charlottesville, Va.,
Contributing Editor, "Anesthesia and Analgesia"

8:30 **HALOTHANE CHALLENGE IN ANIMALS SENSITIZED TO AN INTERMEDIATE HALOTHANE METABOLITE (TRIFLUOACETALDEHYDE) COMPLEXED TO LIVER PROTEIN**

*J. G. Reves, M.D.
L. E. McCraken, Jr., M.D.
R. D. McKay, M.D.
Russell A. Van Dyke, Ph.D.

Discussor: Edward A. Brunner, M.D., Ph.D.

8:55 **PLASMA HEPARIN ACTIVITY AND ANTAGONISM DURING OPEN-HEART SURGERY WITH HYPOTHERMIA**

*Jerry A. Cohen, M.S., M.D.
Evan L. Frederickson, M.D.
Joel A. Kaplan, M.D.

Discussor: D. David Glass, M.D.

9:20 **THE EFFECTS OF NITROUS OXIDE ON CARDIOVASCULAR DYNAMICS DURING ENFLURANE ANESTHESIA IN MAN**

*George M. Bennett, M.D.
Edward A. Loeser, M.D.
Ryohei Kawamura, M.D.
Theodore H. Stanley, M.D.

Discussor: Constance L. Graves, M.D.

9:45 **TRANSIENT EEG ABNORMALITIES FOLLOWING ENFLURANE ANESTHESIA**

Kim Burchiel, B.S.
James Stockard
Roderick Calverley, M.D.
N. Ty Smith, M.D.

Discussor: Leonard C. Jenkins, M.D.

10:10 — — — **INTERMISSION** — — —

11:00 **LEFT HEART DEVICE: EARLY CLINICAL EXPERIENCES WITH MANAGEMENT OF THE POSTPERFUSION LOW CARDIAC OUTPUT**

*George Silvay, M.D.
R. S. Litwak, M.D.
S. B. Lukban, M.D.
R. A. Jurado, M.D.

Discussor: J. Earl Wynands, M.D.

11:25 **HEMODYNAMIC CHANGES DURING INDUCED HYPOTENSION IN INFANTS AND CHILDREN**

*M. Ramez Salem, M.D.
T. Toyama, M.D.
A. Y. Wong, M.D.
Edward J. Bennett, M.D.

Discussor: E. Paul Didier, M.D.

*Will present paper.

Tuesday, March 16 - Scientific Program

Morning
Room B

Chairman: Edwin S. Munson, M.D., Gainesville, Florida,
Member of Board of Trustees, I.A.R.S.

8:30 **STRESSING THE LIPID SOLUBILITY—POTENCY CORRELATION WITH A NEW INHALED AGENT: THIOMETHOXYFLURANE**

*Yasumasa Tanifuji, M.D.
Edmond I. Eger, II, M.D.
Ross C. Terrell, Ph.D.

Discussor: Russell A. Van Dyke, Ph.D.

8:55 **THE ANESTHETIC EFFECT OF OXYGEN**

*Raymond A. Smith, D. Phil.
W. D. M. Paton, D.M., F.R.S., F.R.C.P.

Discussor: C. Ronald Stephen, M.D.

9:20 **ADJUVANTS ALTER ANESTHETIC REQUIREMENTS**

*Robert E. Johnstone, M.D.
Tisha Fendley
Charlene McCarthy
Roger Morrow

Discussor: Cosmo A. DiFazio, M.D., Ph.D.

9:45 **THE INFLUENCE OF HEMODILUTION AND HYPOTHERMIA ON ANESTHETIC BLOOD/GAS PARTITION COEFFICIENT DURING CARDIOPULMONARY BYPASS**

Alfred Feingold, M.D.

Discussor: Harry J. Lowe, M.D.

10:10 — — — INTERMISSION — — —

11:00 **THERMOREGULATORY DEFECT DURING ANESTHESIA**

Richard I. Mazze, M.D.
*Ben A. Hitt, Ph.D.
Thomas L. Cook, M.D.
Jon C. Kosek, M.D.

Discussor: Richard F. Wallin, D.V.M., Ph.D.

11:25 **FENTANYL: CHANGES IN ANESTHETIC POTENCY AND DEPRESSION OF VENTILATORY RESPONSE TO CARBON DIOXIDE**

*Roy M. Bartee, II, LCDR, MC, USNR
John L. Steffenson, Captain, MC, USN

Discussor: Robert F. Hickey M.D.

*Will present paper.

Scientific Exhibits

A CLINICAL EVALUATION OF MICROEMBOLI TRANSFUSION FILTERS DURING SURGERY—E. L. Ellis, M.D., and Angelo Iatridis, M.S.

A TECHNIC OF GENERAL ANESTHESIA FOR BLEPHAROPLASTY AND RHYTIDECTOMY—Herzl Katz, M.D., Roy C. Machida, M.D., D. Gareth Wootton, M.D., and Robert Amonic, M.D.

NEUROLEPTANALGESIA AND LOCAL ANESTHESIA FOR A DYNAMIC APPROACH TO SURGERY OF THE HAND—James C. Erickson, III, M.D., James M. Hunter, M.D., and Larence H. Schneider, M.D.

OBSTETRIC ANESTHESIA AND THE NEWBORN—Gerard W. Ostheimer, M.D., John W. Scanlon, M.D., Milton H. Alper, M.D., Walter U. Brown, Jr., M.D., Jess B. Weiss, M.D., Sanjay Datta, M.D., Rao Mallampati, M.D., and Aron O. Lurie, M.D., Ph.D.

DISTRIBUTION OF LOCAL ANESTHETICS IN THE NEWBORN FOLLOWING MATERNAL EPIDURAL ANESTHESIA—Walter U. Brown, Jr., M.D., and George C. Bell, M.D.

AUTOTRANSFUSION: EXPERIMENTAL AND CLINICAL EXPERIENCE—Glenn W. Geelhoed, M.D., Herbert D. Weintraub, M.D., and Creighton B. Wright, M.D.

ANTICHOLINERGIC DIFFERENCES—A MATTER OF SAFETY—Alon P. Winnie, M.D.

ELECTRICAL HAZARDS IN THE OPERATING ROOM—M. El-Naggar, M.D., E. Kantar, A.A., H. Francis, Ph.D., and V. J. Collins, M.D.

FIBEROPTIC MONITORING OF THE PERIPHERAL PULSE—George C. Bell, M.D.

REGIONAL ANESTHESIA—CURRENT CONCEPTS AND ADVANTAGES—P. C. Lund, M.D., J. C. Cwik, M.D., and R. T. Gannon, M.D.

AMERICAN INDEPENDENCE—ANESTHESIA OR ANAESTHESIA? BI-CENTENNIAL OBSERVATIONS—Keith Murrin, M.B., Kenneth J. Levin, M.D., and Peter V. Scott, M.B.

UPTAKE AND DISTRIBUTION OF ISOFLURANE—Harry J. Lowe, M.D., Thomas N. MacKrell, M.D., and Clair M. Stiles, M.D.

A NEW INJECTABLE ANALGESIC—BUTORPHANOL TARTRATE — FOR MODERATE AND SEVERE PAIN—Allen B. Dobkin, M.D.

ILLUMINATING THE FETAL CIRCULATION—George C. Bell, M.D.

SOURCES AND CONTROL OF ANESTHETIC TRACE GAS LEVELS IN THE OPERATING ROOM—John H. Lecky, M.D., Gordon R. Neufeld, M.D., and James Springstead, D.D.M.

KETAMINE FOR PARTURITION—T. J. Akamatsu, M.D., J. J. Bonica, M.D., and K. Ueland, M.D.

SURFACE ALTERATIONS OF THE TRACHEA ASSOCIATED WITH INTUBATION—Wen-hsien Wu, M.D., M.S., Herman Turndorf, M.D., William N. Bernhard, M.D., and Roland D. Paegle, M.D.

INTRAOPERATIVE AUTOTRANSFUSION—Linda C. Stehling, M.D., Howard L. Zauder, M.D., Ph.D., and Waid Rogers, M.D.

FEATURES OF LONG-TERM ARTIFICIAL VENTILATION (L.T.A.V.), INTERMITTENT MANDATORY VENTILATION (I.M.V.) AND PEEP — Hedayatollah Elyassi, M.D., and Christen C. Rattenborg, M.D.

Tuesday, March 16 - Scientific Program

Afternoon

Chairman: Paul R. Dumke, M.D., Detroit, Michigan,
Member of Board of Trustees, I.A.R.S.
Co-Chairman: Ronald W. Dunbar, M.D., Atlanta, Georgia,
Contributing Editor, "Anesthesia and Analgesia"

1:30 **PEEP AND CPAP: CARDIOPULMONARY EFFECTS DURING SPONTANEOUS VENTILATION**

*Carl L. Sturgeon, Jr., Major, USAF, MC
John B. Downs, M.D.
Michael E. Douglas, Major, USAF, MC
Francis J. Dannemiller, Colonel, USAF, MC

Discussor: Ake Grenvik, M.D.

2:00 **Eleventh Annual Becton, Dickinson and Company Oscar Schwidetzky Memorial Lecture:**

ON THE HISTORY OF IDEAS IN ANAESTHESIA

Leroy David Vandam, M.D.

3:00 **— — — INTERMISSION — — —**

3:30 **CHANGES IN BLOOD CHEMISTRIES FOLLOWING PROLONGED ENFLURANE ANESTHESIA**

*Edmond I. Eger, II, M.D.
R. K. Calverly, M.D.
N. Ty Smith, M.D.

Discussor: Wendell C. Stevens, M.D.

3:55 **CEREBROSPINAL FLUID PRESSURE DURING PNEUMOENCEPHALOGRAPHY AND NITROUS OXIDE INHALATION**

*William L. Paul, M.D.
Edwin S. Munson, M.D.
Jack E. Maniscalco, M.D.

Discussor: Richard A. Elwyn, M.D.

4:20 **DOES FLUORIDE ION PRODUCTION EXPLAIN THE COMPARATIVE TOXICITY OF ENFLURANE, METHOXYFLURANE AND ISOFLURANE?**

*Wendell C. Stevens, M.D.
Anne White, M.S.
Edmond I. Eger, II, M.D.
Richard I. Mazze, M.D.
Ben A. Hitt, Ph.D.
Jon C. Kosek, M.D.

Discussor: Helmut F. Cascorbi, M.D.

*Will present paper.

Wednesday, March 17 - Scientific Program

Morning *Chairman: Emerson A. Moffitt, M.D., Halifax, Nova Scotia,* Vice Chairman of the Board of Trustees, I.A.R.S.

8:30 **CALCIUM, POTASSIUM, AND CITRATE CHANGES DURING RAPID BLOOD TRANSFUSION IN ANESTHETIZED MAN**

*J. Kenneth Denlinger, M.D.
Michael L. Nahrwold, M.D.
Delia R. Bethell, M.S.
W. David Lust, Ph.D.

Discussor: Norig Ellison, M.D.

9:00 **Panel:**

ANESTHESIA FOR THE PATIENT WITH CARDIAC DISEASE

Moderator: Emerson A. Moffitt, M.D.

PREOPERATIVE EVALUATION

Alan H. Goldberg, M.D.

ANESTHETIC MANAGEMENT

Wendell C. Stevens, M.D.

DRUGS IN CARDIAC SUPPORTIVE CARE

Roger D. White, M.D.

ANESTHESIA FOR PATIENTS WITH PACEMAKERS

J. Earl Wynands, M.D.

ANESTHESIA AFTER RECENT INFARCTION

Emerson A. Moffitt, M.D.

DISCUSSION

11:00 — — — **INTERMISSION** — — —

Additional time has been allotted to visit the exhibits.

*Will present paper.

Wednesday, March 17 - Scientific Program

Afternoon: *Chairman: Kenneth K. Keown, M.D., Columbia, Missouri,*
Chairman of the Board of Trustees, I.A.R.S.
Co-Chairman: E. Paul Didier, M.D., Rochester, Minnesota,
Contributing Editor, "Anesthesia and Analgesia"

1:30 **MECHANISM OF CHRONOTROPIC EFFECT OF VOLATILE INHALATION ANESTHETICS**

*Gopal Krishna, M.D.
Raymond R. Paradise, Ph.D.

Discussor: Robert G. Merin, M.D.

2:00 **Fourteenth Annual Baxter-Travenol Lecture:**

EPIDEMIOLOGICAL ANSWERS TO LABORATORY QUESTIONS IN ENVIRONMENTAL CANCER

Irving J. Selikoff, M.D.

3:00 — — — INTERMISSION — — —

3:30 **EFFECT OF KETAMINE ON SURVIVAL RATE FOLLOWING HEMORRHAGE**

David E. Longnecker, M.D.

Discussor: Eugene L. Nagel, M.D.

3:55 **INFLAMMATORY POTENTIAL OF FOREIGN PARTICULATES IN PARENTERAL DRUGS**

*Gordon G. Dorris, M.S.
Brack Bivins, M.D.
Robert Rapp, Pharm.D.
Mark B. Ravin, M.D.
D. L. Weiss, M.D.

Discussor: Ronald W. Dunbar, M.D.

4:20 **PHYSIOLOGIC CONSEQUENCES OF EARLY EXTUBATION IN CARDIAC SURGERY PATIENTS**

*O. Prakash, M.D.
S. H. Meij, M.Sc.
B. Jonson, M.D.
P. G. Hugenholtz, M.D.
W. Hekman, M.D.

Discussor: John H. Tinker, M.D.

*Will present paper.

Thursday, March 18 - Scientific Program

Morning: *Chairman: John T. Martin, M.D., Toledo, Ohio,*
Member of the Board of Trustees, I.A.R.S.
Co-Chairman: Douglas B. Craig, M.D., Winnipeg, Manitoba,
Contributing Editor, "Anesthesia and Analgesia"

8:30 **THE ANESTHETIC POTENCY OF LIDOCAINE IN THE RAT**

*Cosmo A. DiFazio, M.D., Ph.D.
James Niederlehner, M.D.
Robert G. Burney, M.D.

8:45 **SYSTEMIC ABSORPTION AND TISSUE TOXICITY OF BUPIVACAINE (MARCAINE®) FOLLOWING INTERCOSTAL NERVE, BRACHIAL PLEXUS, AND SCIATIC AND FEMORAL NERVE BLOCKS**

*Daniel C. Moore, M.D.
L. E. Mather, M.D.
Phillip O. Bridenbaugh, M.D.
L. Donald Bridenbaugh, M.D.
Robert I. Balfour, M.D.
D. F. Lysons, M.D.
W. G. Horton, M.D.

9:00 **MANAGEMENT OF LOCAL ANESTHETIC-INDUCED CONVULSIONS: CURRENT STATUS**

Rudolph H. de Jong, M.D.

9:15 **DISCUSSION**

9:30 **CLINICAL CLASSIFICATION AND TREATMENT PROGRAM FOR POSTSPINAL HEADACHES—300+ CASES**

Stuart L. Du Pen, M.D.

9:45 **ANALGESIA AND MOTOR FUNCTION IN EPIDURAL BLOCKADE: NEW SOLUTIONS FOR OLD PROBLEMS**

*Philip R. Bromage, M.D.
C. E. B. Norgate, M.B.
R. S. B. Bramwell, M.B.

10:00 **DISCUSSION**

10:15 — — — **INTERMISSION** — — —

*Will present paper.

Thursday, March 18 - Scientific Program

Morning: (Cont'd)

10:45 **ABDOMINAL PAIN: A SOLVENT FOR THE SOLAR PLEXUS**

*Gale E. Thompson, M.D.
Robert Artin, M.D.
L. Donald Bridenbaugh, M.D.
Daniel C. Moore, M.D.

11:00 **A MODEL FOR THE STUDY OF LOCAL ANESTHETIC KINETICS IN MAN**

*Alon P. Winnie, M.D.
Somayaji Ramamurthy, M.D.
Zia Durrani, M.D.
Chen-Hin Tay, M.D.
Kanchan Patel, M.D.

11:15 **DYNAMICS OF COMPOUNDED LOCAL ANESTHETIC MIXTURES IN REGIONAL ANESTHESIA**

*P. Prithvi Raj, M.D.
Jordan Miller, M.D.
Richard Rosenblatt, M.D.
Ronald L. Katz, M.D.

11:30 **COMPARISON OF EFFECTS OF ACUPUNCTURE AND CODEINE ON POSTOPERATIVE DENTAL PAIN**

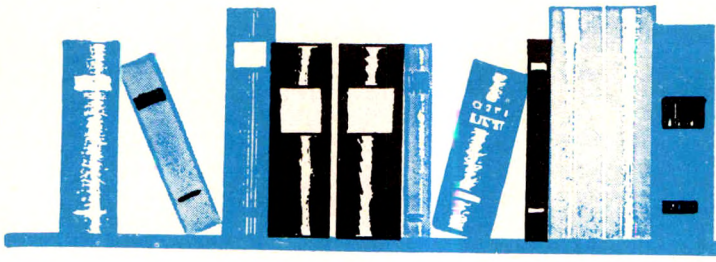
*Y. F. Sung, M.D.
Michael H. Kutner, Ph.D.
F. C. Cerine, D.D.S.
Evan L. Frederickson, M.D.

11:45 **DISCUSSION**

*Will present paper.

NOTE

Program content, as well as days and times of presentation are subject to change, and any changes will be included in the final program distributed at the meeting. The final program will also contain abstracts of the scientific papers, as well as names and professional affiliations of all individuals involved in the preparation, presentation or discussion of the papers.



the book shelf

Public Health Aspects of Critical Care Medicine and Anesthesiology — Safar, Peter, M.D., Editor. Philadelphia, FA Davis Company, Clinical Anesthesia, 1974, vol 10, no 3, 396 pp, price $20.00.

The objective of this contribution to the *Clinical Anesthesia* series is to give the reader, in particular physicians and other health-care professionals, a broad view and assessment of the current systems of medical-care delivery and the associated unsolved problems and their possible solutions. "Public health" in this context refers to community medical-care systems and the planning, implementation, and evaluation of health-care delivery programs.

For the most part, the topics relate directly to the role of the anesthesiologist in health-care delivery; areas of concern include resuscitation and life-support, emergency medical care, and intensive care.

Inclusion of "critical-care medicine" certainly reflects the editor's well-known interests and concern for this area of medical practice—an area to which Dr. Safar has made many and major contributions. In fact, in those chapters authored by Safar, there emerges a rather clear picture and perception of his own philosophies and strongly-worded opinions. For example, on page 15: "In the 1950s disasters were considered mainly from the point of view of nuclear war. Millions of dollars were spent to satisfy the Cold War paranoia of certain governmental agencies, although we lacked the most basic emergency care for everyday needs." Safar knows well from personal experience, some of which he shares in this book, the frustrations of attempting to upgrade emergency services in the face of apathy and frank and bitter opposition.

Here are some of the many areas surveyed: Centralization of hospital care for the critically ill; hospital and emergency facility categorization; current status of respiratory-care services in the United States; surgical and anesthesia workloads, anesthesia mortality; anesthesia manpower and allied health personnel in anesthesia; outpatient anesthesia; and anesthesia costs. Of course, cardiopulmonary resuscitation and emergency and critical-care systems are discussed at length.

It should be apparent that there is something for nearly everyone in this volume. In spite of multiple authorship, there is very little duplication, perhaps because each chapter "stands on its own" and covers distinct yet related material. It is an informative text and will be useful as a resource for many areas of anesthesiology and critical-care medicine.

Roger D. White, M.D.
Department of Anesthesiology
Mayo Clinic
Rochester, Minnesota

* * *

Life-Threatening Emergencies in the Dental Practice — Schijatschky, Milan M., Berlin, Chicago, Quintessence Books, 1975, 163 pp.

To quote from the introductory paragraph of this interesting and informative book: "There is no such thing as a life-threatening emergency specific to the dental office," is good reason for the dental practitioner to become familiar with any situations that may require emergency measures in his office.

The author has presented this subject in considerable depth and has included much valuable information and directives for the benefit of the dental practitioner.

This should be a very useful source of information for students and practitioners in the dental profession.

IN THE NEXT ISSUE

Scientific Articles

March-April, 1976

A TECHNIC OF GENERAL ANESTHESIA FOR BLEPHAROPLASTY AND RHYTIDECTOMY—Herzl Katz, M.D., Roy C. Machida, M.D., D. Gareth Wootton, M.D., and Robert Amonic, M.D., Los Angeles, California.

CARDIOVASCULAR DYNAMICS AFTER LARGE DOSES OF FENTANYL AND FENTANYL PLUS NITROUS OXIDE IN THE DOG—Wen-Shin Liu, M.D., Arun V. Bidwai, M.D., Theodore H. Stanley, M.D., and Jesus Isern-Amaral, M.D., Salt Lake City, Utah.

CIRCULATORY CHANGES IN PATIENTS WITH CORONARY ARTERY DISEASE FOLLOWING THIAMYLAL-SUCCINYLCHOLINE AND TRACHEAL INTUBATION DURING ANESTHESIA—Robert K. Stoelting, M.D., and Christine Peterson, Indianapolis, Indiana.

ANAPHYLAXIS AND CHEMONUCLEOLYSIS: GUIDELINES FOR MANAGEMENT—Dean H. Morrow, M.D., Houston, Texas.

CARDIOVASCULAR EFFECTS OF CANNABINOL DURING ORAL SURGERY—John M. Gregg, D.D.S., Ph.D., Robert L. Campbell, D.D.S., Kenneth J. Levin, M.S., M.D., and Riley A. Elliott, B.S., Chapel Hill, North Carolina.

MANAGEMENT OF INTRACTABLE PAIN IN ADIPOSIS DOLOROSA WITH INTRAVENOUS ADMINISTRATION OF LIDOCAINE—Tadashi Iwane, M.D., Masanori Maruyama, M.D., Michiko Matsuki, M.D., Yusuke Ito, M.D., and Koki Shimoji, M.D., Niigata, Japan.

RESECTION OF STENOTIC TRACHEA: A CASE PRESENTATION—C. Paul Boyan, M.D. and Paul A. Privitera, C.R.N.A., Richmond, Virginia.

INCIDENCE OF PROLONGED PAIN RELIEF FOLLOWING ACUPUNCTURE—Peter K. Y. Lee, M.D., Jerome H. Modell, M.D., Thorkild W. Andersen, M.D., and Segundina A. Saga, M.D., Gainesville, Florida.

THE INTERACTION BETWEEN D-TUBOCURARINE, PANCURONIUM, POLYMYXIN B, AND NEOSTIGMINE ON NEUROMUSCULAR FUNCTION—Linda S. Van Nyhuis, Ronald D. Miller, M.D., and Richard P. Fogdall, M.D., San Francisco, California.

ANESTHETIC CONSIDERATIONS IN DIFFUSE BLEEDING DIATHESIS OF UNCERTAIN ORIGIN—F. Y. Dalal, FFARCS, E. J. Bennett, FFARCS, E. M. Grundy, FFARCS, and S. Younes, M.D., Chicago, Illinois.

BACTERIOLOGIC ASPECTS OF EPIDURAL ANALGESIA—Francis M. James, III, M.D., Richard H. George, M.B., Ch.B., MRC Path., Hamid Naiem, M.B., MRCOG, and Gary J. White, FIMLT., Winston Salem, North Carolina and Birmingham, England.

THE INFLUENCE OF SUCTION CATHETER TIP DESIGN ON TRACHEOBRONCHIAL TRAUMA AND FLUID ASPIRATION EFFICIENCY—William J. Link, Ph.D., Edmund E. Spaeth, Ph.D., William M. Wahle, M.D., William Penny, M.S., and John L. Glover, M.D., Indianapolis, Indiana and Glendale, California.

FAILURE TO INDUCE HEPATIC PATHOLOGY IN ANIMALS SENSITIZED TO A HALOTHANE METABOLITE AND SUBSEQUENTLY CHALLENGED WITH HALOTHANE—J. G. Reves, M.D., and Linton E. McCracken, Jr., M.D., Bethesda, Maryland.

A POTENTIAL IGNITION SOURCE IN THE OPERATING ROOM—Edward F. Anderson, LCDR, USN (MC), Great Lakes, Illinois.

THE EFFECTS OF DOXAPRAM ON CEREBRAL BLOOD FLOW AND PERIPHERAL HEMODYNAMICS IN THE ANESTHETIZED AND UNANESTHETIZED GOAT—David J. Miletich, Ph.D., Anthony D. Ivankovich, M.D., Ronald F. Albrecht, M.D., Roger F. Bonnet, M.D., and Charles R. Reimann, M.D., Chicago, Illinois.

"PENTAZEPAM" (PENTAZOCINE + DIAZEPAM) SUPPLEMENTING LOCAL ANALGESIA FOR LAPAROSCOPIC STERILIZATION—J. Antonio Aldrete, M.D., Shirley T. Liem, M.D., Donald J. Carrow, M.D., and Mary K. Watts, CRNA, Louisville, Kentucky.

ATYPICAL PSEUDOCHOLINESTERASE: A CLINICAL REPORT—Erwin Lear, M.D., Cassim Jadwat, M.D., Lucy Bough, M.D., and Paz Fernandez, M.D., Jamaica, New York.

ANESTHETIC CONSIDERATIONS IN PATIENTS WITH GAS GANGRENE—Michael J. Laflin, M.D., Raymond E. Tobey, M.D., and J. G. Reves, M.D., Bethesda, Maryland.

A COMPARATIVE STUDY OF ENFLURANE AND HALOTHANE USING SYSTOLIC TIME INTERVALS—Joel A. Kaplan, M.D., Edward D. Miller, M.D., and Daniel R. Bailey, M.D., Atlanta, Georgia and San Antonio, Texas.

THOUGHTS ABOUT MEDICAL WRITING. XXIV—Charles G. Roland, M.D., Rochester, Minnesota.

MANAGEMENT OF A PARTURIENT WITH CARDIAC VALVE PROSTHESIS—Demir M. Saka, M.D., and Gertie F. Marx, M.D., Bronx, New York.

PROLONGED TRANSLARYNGEAL INTUBATION VERSUS AN EARLY TRACHEOSTOMY IN ACUTE RESPIRATORY FAILURE—Moustafa El-Naggar, M.D., Seshadri Sadagopan, M.D., Harry Levine, Ph.D., Harvey Kantor, M.D., and Vincent J. Collins, M.D., Chicago, Illinois.

SURVIVAL FOLLOWING MASSIVE PULMONARY HEMORRHAGE COMPLICATING PULMONARY EMBOLECTOMY—Stuart Wollman, M.D., and Lawrence G. Kushins, M.D., New Hyde Park, New York.

EFFECT OF $PaCO_2$ ON OXYGEN CONSUMPTION DURING CARDIOPULMONARY BYPASS IN MAN—Richard W. Patterson, M.D., Los Angeles, California.

CASE HISTORY NUMBER 89. A LIFE THREATENING COMPLICATION OF CRICOTHYROID MEMBRANE PUNCTURE —Y. K. Poon, M.B., B.S., F.F.A.R.C.S., Donald H. Reimer, M.D. FRCP (C) and Douglas B. Craig, M.D. FRCP (C).

Brief Reports:

ACUTE CARDIOVASCULAR COLLAPSE AFTER INTRAVENOUS PHYTONADIONE—Luke M. Kitahata, New Haven, Connecticut.

AN UNUSUAL PROBLEM IN NASOTRACHEAL EXTUBATION—Gary S. Sklar, M.D., Antonio E. Alfonso, M.D., and Benton D. King, M.D., Brooklyn, New York.

A SIMPLE METHOD OF INSERTING A NASOGASTRIC TUBE DURING ANESTHESIA—Anis Baraka, M.D., Beirut, Lebanon.

A Guide for Authors

Anesthesia and Analgesia . . . Current Researches invites original manuscripts on subjects pertinent to the specialty of anesthesiology. Original articles accepted for publication, or papers presented at the Society's annual scientific meetings which subsequently may be published in the Journal, become the property of the International Anesthesia Research Society. Reproduction in whole or in part is not permitted except by written consent of the publisher and the author.

Submit manuscripts in triplicate to—
T. H. Seldon, M.D., Editor
Kahler East, Suite C
Rochester, Minnesota 55901, U.S.A.

All papers are reviewed by the Editorial Board and other selected referees. If accepted for publication, editorial revisions may be made to aid clarity and understanding without altering the meaning. Edited copy is submitted to authors for approval before it is sent to the printer. Page proof will be submitted to authors for final approval. Reprint order forms will accompany page proof.

Titles should be concise but informative, with thought given to the use of key words for indexing. Ninety characters, including punctuation and spaces, should be sufficient.

Coauthors' names should be followed by the major degree, professional affiliation, and address.

Abstract: On the first page of manuscript, an abstract of from 50 to 250 words, according to length of article, but not exceeding one double-spaced typed page, should describe purpose, methods, results, and conclusions, as succinctly as possible. This replaces both former Capsule Review and Summary, but is the same in content and format.

Type manuscript (in triplicate) on 8½ x 11-inch white paper, with 1½ inch margins at top, bottom, and both sides. Double space ALL typing, including references, legends and footnotes.

References: About 20 references are acceptable. In extensive reviews of the literature, readers will be advised that longer reference citations can be obtained from author. Citations should include (1) last name of author followed by initials without internal punctuation; (2) commas separate names and initials of authors; (3) four or more authors are designated as "et al;" (4) journal name is abbreviated according to Index Medicus style; (5) references from books show (a) city of publication, name of publisher, date of publication, after book title; (6) journal references give volume, first and last page numbers, year. (See previous issues of *Anesth & Analg* for style.)

Tables should be self-explanatory and should supplement, not duplicate, the text.

Photographs should have sharp contrast, be on *glossy* paper unmounted, and 4 by 5 inches or larger. *Polaroid prints damage easily in handling and thus may reproduce indistinctly. Glossy prints are preferred.* Submit photographs of roentgenograms with contrasts as in original and sharply defined; "TOP" must be identified. All illustrative materials, charts, etc., must be submitted in triplicate, clearly numbered according to text and legend.

Lettering on charts and graphs must be large enough to be legible when reduced in size. Curves, scatter dots, etc., should contrast with reference lines.

Drawings must be in black (India) ink on white background and should be of professional quality.

Legends for illustrations should be concise and typed on one page. Legends for photomicrographs should show stain and magnification data.

Drug names used in the text should be generic unless trade names are essential to the discussion.

Multiple Publication: To avoid violating existing copyrights, a statement should accompany each submitted article indicating that the material in question:

1. Has not been simultaneously submitted to another journal.
2. Has not been previously published elsewhere.

a. Abstracts of 400 words or less do not constitute prior publication.

b. A report issued by requirement of a governmental agency or comparable granting institution does not constitute prior publication.

c. Extracting by news media does not constitute prior publication unless all vital tables and pertinent conclusions are involved or unless such publication was actively solicited by the authors.

Legal considerations require letters of permission from authors and publishers for use of illustrations or quotations originally appearing elsewhere, and also written permission for use of photographs of identifiable patients. Identifying information, such as names, initials, hospital numbers, and dates, must be avoided.

When experimentation involving human subjects is reported, an appropriate statement regarding informed consent should be made.

Case reports should include only significant data. Laboratory findings should be restricted to those pertinent to the discussion.

Symbols used for respiratory physiology should follow Fed. Proc. 9:602, 1950.

Explanation of abbreviations and symbols used within the text should be added as a footnote.

Example: torr: Unit of pressure of 1 mm. of mercury at 0° C. and standard gravity.

CHECK LIST

- ☐ Title
- ☐ Authors
- ☐ Abstract
- ☐ Text
- ☐ Tables
- ☐ References
- ☐ Figures
- ☐ Legends

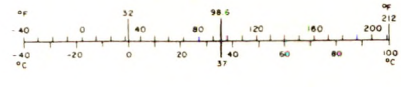
Manuscripts and all illustrations should be mailed flat, *in triplicate*, with cardboard protection. The author should retain one complete copy, including tables and illustrations.

Metric Conversions

HEIGHT			WEIGHT	
Cm	Feet	Inches (approx.)	Kilograms	Pounds
15	0 ft.	6 in.	1	2.2
30	1 ft.	0 in.	5	11
45	1 ft.	8 in.	10	22
60	1 ft.	11½ in.	15	33
75	2 ft.	5½ in.	20	44
105	3 ft.	5 in.	25	55
115	3 ft.	9 in.	30	66
120	3 ft.	11 in.	35	77
125	4 ft.	1 in.	40	88
130	4 ft.	3 in.	45	99
135	4 ft.	5 in.	50	110
140	4 ft.	7 in.	55	121
145	4 ft.	9 in.	60	132
150	4 ft.	11 in.	65	143
155	5 ft.	1 in.	70	154
160	5 ft.	3 in.	75	165
165	5 ft.	5 in.	80	176
170	5 ft.	7 in.	85	187
175	5 ft.	9 in.	90	198
180	5 ft.	11 in.	95	209
185	6 ft.	1 in.	100	220
190	6 ft.	3 in.	105	231
195	6 ft.	5 in.	110	242
200	6 ft.	7 in.	115	253
205	6 ft.	9 in.	120	264
210	6 ft.	11 in.	125	275
215	7 ft.	1 in.		

APPROXIMATE CONVERSIONS FROM METRIC MEASURES

Symbol	When You Know	Multiply by	To Find	Symbol
	LENGTH			
mm	millimeters	0.04	inches	in
cm	centimeters	0.4	inches	in
m	meters	3.3	feet	ft
m	meters	1.1	yards	yd
km	kilometers	0.6	miles	mi
Symbol	When You Know	Multiply by	To Find	Symbol
	MASS (weight)			
g	grams	0.035	ounces	oz
kg	kilograms	2.2	pounds	lb
t	tonnes (1000 kg.)	1.1	short tons	
Symbol	When You Know	Multiply by	To Find	Symbol
	TEMPERATURE (exact)			
°F	Farenheit temperature	5/9 (after subtracting 32)	Celsius temperature	°C



Anesthesia and Analgesia CURRENT RESEARCHES

BACK ISSUES AVAILABLE

Available at $3.00 Per Issue

Vol.	Year	Numbers Available						Vol.	Year	Numbers Available					
33	1954	–	2	3	4	5	6	41	1962	–	2	3	–	5	6
34	1955	1	2	3	4	5	6	42	1963	–	–	3	4	5	6
35	1956	1	2	3	4	5	6	43	1964	–	2	–	–	–	6
36	1957	–	–	–	–	–	6	44	1965	–	2	3	4	5	6
37	1958	1	2	3	4	5	6	45	1966	–	2	–	–	–	6
38	1959	–	2	3	4	–	6	46	1967	–	–	3	–	–	6
39	1960	–	–	3	4	5	6	47	1968	–	–	3	4	5	6
40	1961	–	–	3	4	5	6	48	1969	1	2	3	–	5	–

Available at $4.50 Per Issue

Vol.	Year	Numbers Available						Vol.	Year	Numbers Available					
49	1970	1	–	–	–	5	6	52	1973	1	2	3	4	5	6
50	1971	1	2	3	–	–	–	53	1974	–	2	3	4	–	–
51	1972	–	2	3	–	–	6	54	1975	1	2	3	–	5	6

SINGLE ISSUES PRIOR TO 1954: Write to publisher at address below for listing of issues available at $2.00 each.

BOUND VOLUMES AVAILABLE: $8.00—For Years 1947, 1948, 1949; $10.00—For Years 1953, 1955

OTHER PUBLICATIONS AVAILABLE:

"Basic and Clinical Physiology of the Liver" (Supplement to Sept.-Oct. 1965 issue)—$3.00.

Ten-Year (1960-1969) Cumulative Index—$3.00.

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, Ohio 44122

Please send me the publications circled above, or listed hereunder:

☐ Check for $_____ enclosed.

☐ Please send bill with understanding that ordered material will be sent when payment is received.

Name_____

Address_____

City, State, Zip_____

When you need to know

DINAMAP for **non-invasive,** routine monitoring of arterial pressure.

Using: An ordinary pressure cuff with no transducer. Easily attached to any limb.

Provides: Automatic determination and digital display of mean arterial pressure.

Write or call for your demonstration.

Applied Medical Research
6 Columbia Drive
Tampa, Fla. 33606
(813) 251-8390

A "quick recovery" anesthetic for short surgical procedures

Ethrane® (enflurane) fulfills your anesthetic requirements for short surgical procedures.

Fast Induction, Rapid Recovery. The low blood/gas partition coefficient of ETHRANE (1.91 at 37°C) assures rapid patient induction with minimal excitation. Its mild, pleasant odor is highly acceptable and ETHRANE does not stimulate increased salivation or affect bronchomotor tone.[1] Pharyngeal and laryngeal reflexes can be quickly and easily obtunded. Following anesthesia, because of its low blood solubility, ETHRANE is promptly eliminated at the lungs, permitting rapid emergence and recovery.[2]

Stable Cardiac Rhythm. Cardiac rhythm usually remains normal during ETHRANE anesthesia and is not altered even with elevations in arterial carbon dioxide.[3] Although nodal or atrial arrhythmias occasionally appear, ventricular extrasystoles are rare. Heart rate is sustained at preanesthetic levels. Bradycardia or tachycardia do not normally occur. Blood pressure tends to be reduced with induction, but this effect is reversed with surgical stimulation.[4]

Excellent Muscle Relaxation. At clinical concentrations, ETHRANE usually provides muscle relaxation sufficient for lower abdominal procedures. In addition, relaxation is often adequate for procedures of the upper abdomen. If greater relaxation is required, its potentiation of nondepolarizing relaxants reduces the dosage of such adjunctive neuromuscular blocking agents.[4]

Few Anesthetic Aftereffects. Following cessation of anesthesia with ETHRANE, recovery is rapid, uneventful, and complete. Postoperative return of adequate pulmonary ventilation is rapid.[1] Nausea, vomiting, and delirium are rare. Usually there is an early return of lucidity, desire for fluids, and generally a feeling of well-being.[1,5]

WARNING: Motor activity exemplified by movement of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia. For additional warnings, contraindications, and precautions, see following page.

Films Available for Medical Education. As a service to the anesthesia profession, Ohio Medical Products has available, without charge, motion pictures for use in continuing medical education. Topics include such areas as "Management of Ambulatory Surgical Procedures" and "The Use of ETHRANE." To arrange for a personal or group showing, contact your OHIO Anesthetic Representative, or write to our Communications Department in Madison, Wisconsin.

Ethrane®
(enflurane)

Versatile in Concept–Versatile in Performance

Ohio Medical Products
3030 AIRCO DRIVE
MADISON, WISCONSIN 53701

AIRCO®

See following page for full disclosure

Ethrane® (enflurane) Versatile in concept... Versatile in performance.

CAUTION: Federal Law Prohibits Dispensing without Prescription

Description: ETHRANE (enflurane) is a nonflammable anesthetic agent. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether, and its structural formula is:

Some physical constants of the compound are:

Molecular weight	184.5
Boiling point 760 mm Hg.	56.5°C
Refractive index n_D^{20}	1.3026-1.3030
Specific gravity 25°/25°C	1.517
Vapor pressure in mm Hg.**	20°C 174.5 25°C 217.7 36°C 345.2

**Equation for calculation of enflurane vapor pressures:

$$\log_{10} P = A + \frac{B}{T}$$

A = 7.967
B = −1678.4
T = °C + 273.16 (Kelvin)

Partition coefficients @ 37°C	
Water-gas	0.82
Blood-gas	1.91
Oil-gas	98.5
Partition coefficients @ 25°C— rubber and plastic	
Conductive rubber	74.0
Butyl rubber	90.0
Polyvinylchloride	120.0
Polyethylene	∼2.0
Polyurethane	∼1.5
Polyolefin	∼1.2
Butyl acetate	∼3.0
Solubility of enflurane in H_2O at 22°C	0.275%
Solubility of H_2O in enflurane	0.13%
Purity by gas chromatography	>99.9%
Flammability in air	None
Flammability in oxygen (Entire concentration range to saturation at 71 and 113°F and 743 mm Hg. pressure.)	None
M.A.C. (Minimum alveolar concentration)	
Man with pure oxygen	1.68
Man with 70% nitrous oxide	0.56 (est.)

ETHRANE is a clear, colorless, stable liquid without added chemical stabilizers. ETHRANE has a mild, sweet odor. Storage of samples in indirect sunlight in clear, colorless glass for a five year period, as well as direct exposure for 30 hours to a 2 amp, 115 V., 60 cycle long wave U.V. light, produced no changes in composition detectable by gas chromatography. ETHRANE in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed none of the alkali, indicative of strong base stability. ETHRANE does not decompose in contact with soda lime. ETHRANE does not attack aluminum, tin, brass, iron or copper.

Actions: ETHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ETHRANE are rapid. ETHRANE does not appear to stimulate excess salivation or tracheobronchial secretions, or affect bronchomotor tone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ETHRANE. ETHRANE reduces ventilation as depth of anesthesia increases. ETHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm. ETHRANE sensitizes the myocardial conduction system to epinephrine in dog and can produce serious arrhythmias. Comparable information in man is not available.

Muscle relaxation is adequate for intra-abdominal operation at normal levels of anesthesia. Should greater relaxation be necessary, minimal doses of muscle relaxants may be used. All commonly used muscle relaxants are compatible with ETHRANE. **The nondepolarizing muscle relaxants are markedly potentiated.** Neostigmine does not reverse the direct effect of ETHRANE.

Biotransformation of ETHRANE (enflurane) in man results in low levels of serum fluoride ions averaging 15 mM/L. These levels are well below the 50 mM/L seen to produce renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation.

Indications: ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

Contraindications: Seizure disorders (see WARNINGS).

Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.

Warnings: Increasing depth of anesthesia with ETHRANE (enflurane) produces a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by hyperventilation producing low arterial carbon dioxide tension. The pattern serves as a warning that depth of anesthesia is excessive. Cerebral blood flow and metabolism studies in normal volunteers during seizure patterns show no evidence of cerebral hypoxia, and recovery appears to be uncomplicated.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. With deep levels of anesthesia, more marked hypotension and respiratory depression are encountered.

The action of nondepolarizing relaxants is augmented by ETHRANE. Less than the usual amounts of these drugs should be used. The time for recovery from the myoneural effect of these relaxants is greater in the presence of ETHRANE than for other commonly used anesthetics.

The safety of the use of epinephrine topically and subcutaneously has not been established in man.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

Precautions: Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ETHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ETHRANE.

Adverse reactions: 1. Motor activity exemplified by movement of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia. 2. Hypotension and respiratory depression have been reported. 3. Arrhythmias, shivering, nausea, and vomiting have been reported. 4. Elevation of the white blood count has been observed. It has not been determined whether this is related to ETHRANE or to surgical stress.

Dosage and administration: The concentration of ETHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ETHRANE;
b) vaporizers from which delivered flows can easily and readily be calculated.

Maintenance concentration should not exceed 3%. Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ETHRANE and the heart rate remains constant. The use of anticholinergic drugs is a matter of choice.

Induction: Induction may be achieved using ETHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ETHRANE mixture. In general, inspired concentrations of 3.5-4.5% ETHRANE produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be attained with 1.5-3.0% concentration. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm range is preferred to hyper- or hypoventilation in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ETHRANE concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration; establish that the airway is clear and initiate assisted or controlled ventilation with pure oxygen as circumstances dictate.

Administration equipment: ETHRANE (enflurane) may be administered from a flow-through type vaporizer manufactured and specifically calibrated for ETHRANE. Vaporizers which deliver saturated vapor at reasonable flows but are not specifically calibrated for ETHRANE may be used.

ETHRANE contains no stabilizer. Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Packaging: ETHRANE (enflurane) is packaged in 125 and 250 ml. amber bottles. No additives or stabilizers are present.

References:

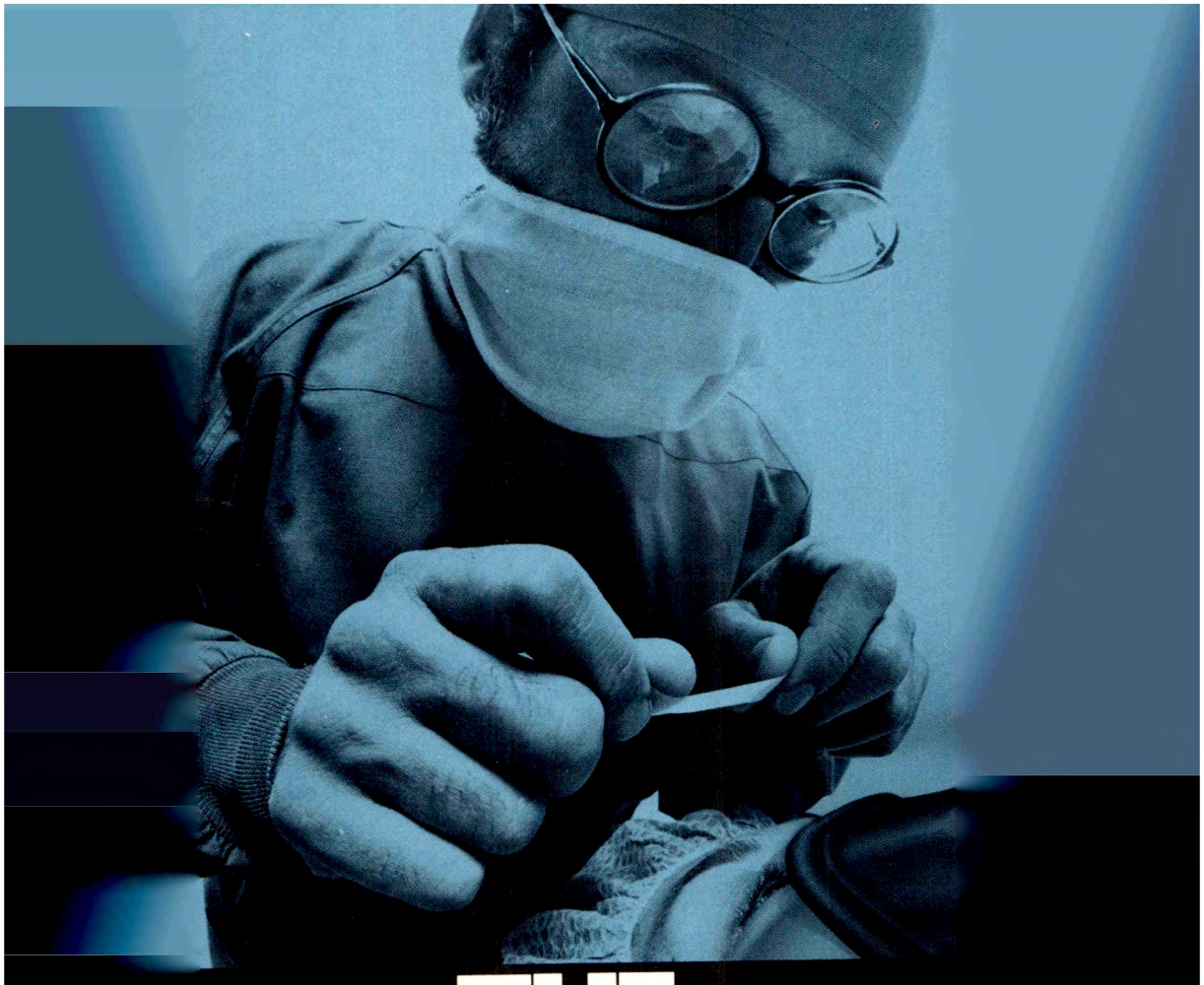
1. Dobkin, A. B., et al: Ethrane (Compound 347) Anesthesia: A Clinical and Laboratory Review of 700 Cases. Anesthesia and Analgesia **48**:477-494, May-June, 1969.

2. Torri, G., et al: Uptake and Elimination of Enflurane in Man. A Comparative Study between Enflurane and Halothane. British Journal of Anaesthesia. **44**:789-794, August, 1972.

3. Marshall, B.E., et al: Some Pulmonary and Cardiovascular Effects of Enflurane (Ethrane) Anesthesia with Varying $PaCO_2$ in Man. British Journal of Anaesthesia. **43**:996-1002, November, 1971.

4. Botty, C., et al: Clinical Experiences with Compound 347, A Halogenated Anesthetic Agent. Anesthesia and Analgesia **47**:499-505, September-October, 1968.

5. Lebowitz, M.H., et al: Clinical Investigation of Compound 347 (Ethrane). Anesthesia and Analgesia. **49**:1-10, January-February, 1970.



THE VULNERABLE EYE.

be® protects the vulnerable eye of the anesthetized patient.

e under-protected eye is threatened during general anesthesia. Tape alone r patient's eye vulnerable to dehydration and corneal erosion. And with d ointments, you unnecessarily risk allergic reactions and possible long-te on.

ri-Lube meets your need for a safer, more sophisticated method of prote cating the eye. Either on its own or as an adjunct to taping. It's the first nc d, sterile ophthalmic ointment specifically designed to lubricate and prote l do nothing more.

act, ophthalmologists have established Lacri-Lube as their lubricant-prote nenever an eye is jeopardized by exposure or dehydration. And the rapid gical use indicates that Lacri-Lube fulfills the same need among anesthesi ri-Lube is the ophthalmic for anesthesia.

en you consider the alternatives, make a better choice.

ALLERGAN
Irvine, CA 92664

um, mineral oil, nonionic lanolin derivatives, chlorobutanol (chloral derivative as preservative) 0.5%. St

Take the **Excessive Anxiety** out of **Anesthesia**

Vistaril I.M. (hydroxyzine HCl) helps allay the anxiety that may complicate premedication, induction and recovery room emergence.

It has no significant depressant effects on respiratory or circulatory function and often reduces postoperative emesis.

Vital signs are seldom impaired. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.

And, because it may enhance the effect of injectable analgesics, requirements of narcotic and nonnarcotic analgesics, such as meperidine, morphine sulfate and pentazocine, may be reduced.

Vistaril I.M. is physically compatible with most commonly used analgesics, and can be mixed with them in the same syringe.

Alone, or as an adjunct for use with injectable analgesics, the maximum recommended dosage of Vistaril I.M. is 100 mg. While the analgesic dosage needed will usually be reduced, the actual dosage of Vistaril I.M. should be titrated against the individual patient's clinical response.

Vistaril® I.M.
(hydroxyzine HCl)
100 mg./2 ml., 50 mg./ml. and 25 mg./ml. Vials and Isojects®

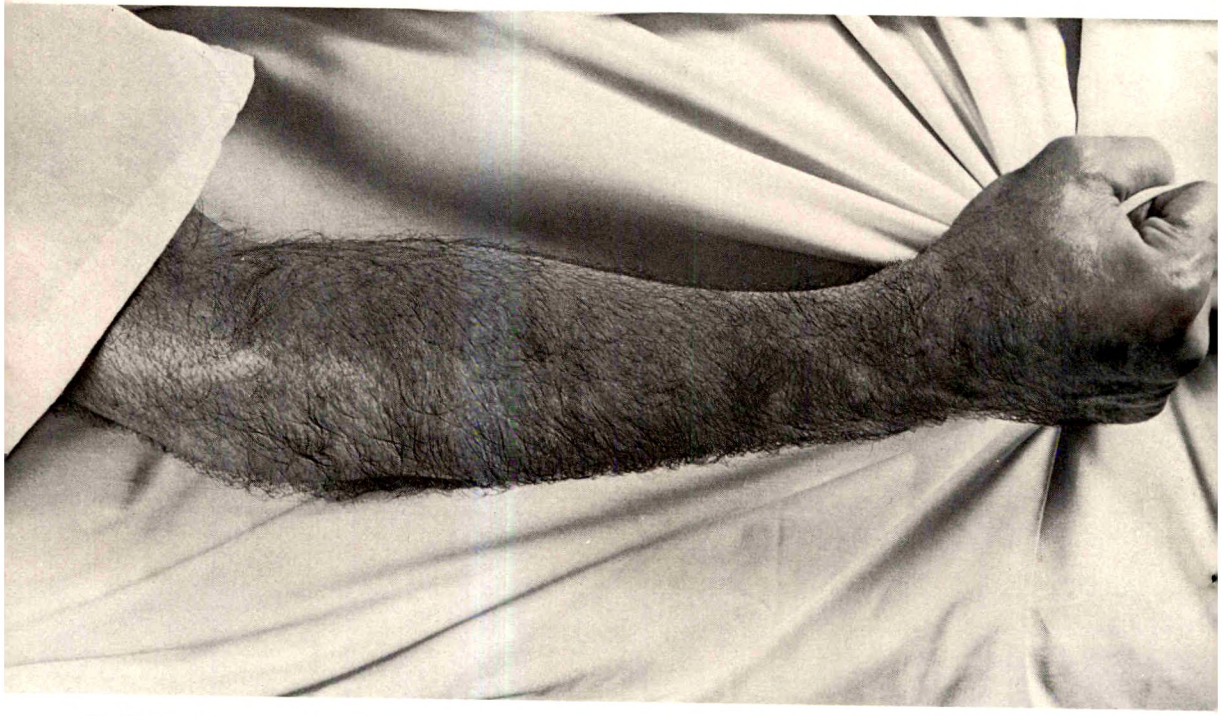
Pfizer
LABORATORIES DIVISION
PFIZER INC.

Please see Brief Summary on following page for contraindications, precautions and adverse reactions.

Vistaril® I.M.
(hydroxyzine HCl)

100 mg./2 ml., 50 mg./ml. and 25 mg./ml.
Vials and Isojects®

Calm
Before Anesthesia... In Recovery



Brief Summary
VISTARIL® (hydroxyzine hydrochloride) Intramuscular Solution
For Intramuscular Use Only

Contraindications: Hypersensitivity to hydroxyzine. The solution for intramuscular use *must not* be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate. Until adequate data are available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: *Hydroxyzine may potentiate the action of central nervous system depressants such as narcotics and barbiturates.* In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used.

Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscle of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in c to minimize the possibility of damage to the sciatic nerve. The deltoic area should be used only if well developed, such as in certain adults older children, and only with caution to avoid radial nerve injury. Injections should not be mac'e in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid intravascular inject

Adverse Reactions: Drowsiness may occur; if so, it is usually transit and may disappear in a few days of continued therapy or upon dosag reduction. Dryness of the mouth may occur with higher doses. Involu tary motor activity, including rare instances of tremor and convulsion has been reported, usually with higher than recommended dosage.

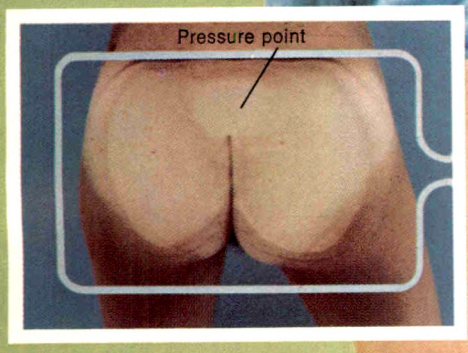
Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg./n 10 ml. vial; 50 mg./ml.—2 ml. and 10 ml. vial; Isoject®, 25 mg./ml. ar 50 mg./ml., 1 ml. fill; 100 mg./2 ml., 2 ml. fill.

Military Depot: NSN 6505-00-052-1367 (50 mg./ml., 10 ml. vial)
VA Depot: NSN 6505-00-052-1367B (50 mg./ml., 10 ml. vial)

More detailed professional information available on request.

Pfizer **LABORATORIES DIVISION**
PFIZER INC.

Electrosurgical burn hazard: unsafe current densities created by pressure points.



Subject viewed through transparent plastic.

Remedy: Ground the patient using the American Electro·Surgical Grounding Pad system.

When grounding a patient with a conventional metal dispersive plate, bony protuberances can create pressure points which result in uneven patient contact. Any pressure point can become the site of burn-inducing high current densities.

The American Electro-Surgical Grounding Pad virtually eliminates the hazards associated with pressure points because it replaces patient-to-metal contact with a column of low impedance gel: This non-metal, *non-pressure* interface between patient and grounding device is efficient and reliable.

And since the Grounding Pad does away with patient-to-metal contact, it eliminates many of the other hazards associated with metal grounding devices—hazards such as bent corners and irregularities in the conductive surface.

- The Grounding Pad is pregelled, self-adhering and disposable, so it is as convenient to use as it is reliable.

In the few short years since its introduction, the American Electro-Surgical Grounding Pad system has been chosen over dispersive plates for more than 6,000,000 electrosurgical procedures.

A clinical trial will demonstrate why.

Please contact your American Hospital Supply or NDM representative for a clinical trial, including a total inservice, for your evaluation of the American Electro-Surgical Grounding Pad system.

For a comprehensive booklet describing the Electro-Surgical Grounding Pad system, please write to: NDM Department D, 3040 East River Road, Dayton, Ohio 45439.

ndm Manufactured in U.S.A. by NDM Corporation, Dayton, Ohio 45439

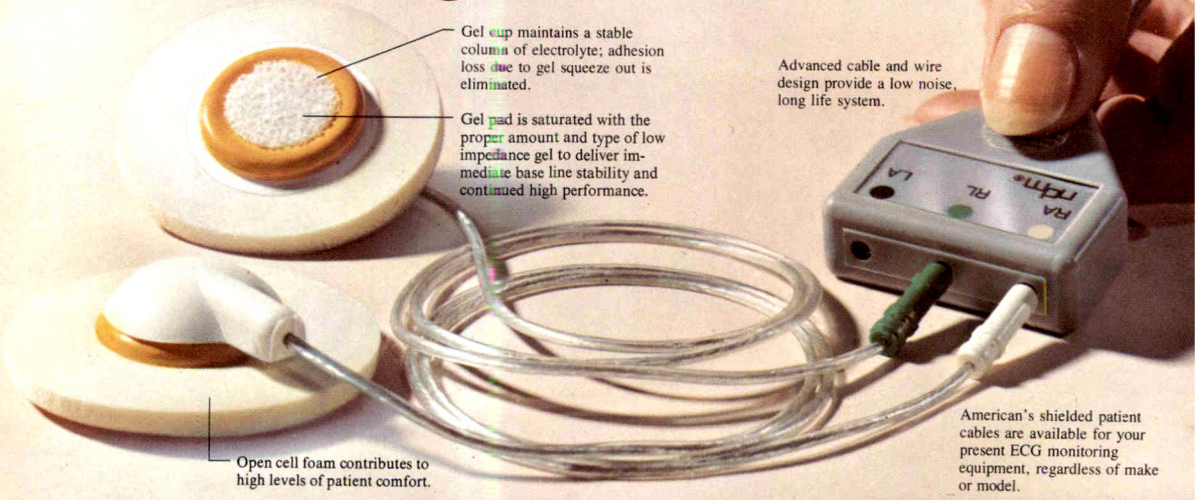
Available through

AMERICAN HOSPITAL SUPPLY

DIVISION OF AMERICAN HOSPITAL SUPPLY CORPORATION - General Offices: 1450 Waukegan Road, McGaw Park, Illinois 60085

Catalog Number 65418-010 THE ELECTRO-SURGICAL GROUNDING PAD IS PROTECTED BY NDM CORP. BY U.S. PATENT 3,846,600

American's O.R. Electrode System brings highest performance to your operating and recovery room ECG monitoring.



So-called "all-purpose" electrodes are bound to have built-in compromises. That's why American offers a full line of ECG monitoring electrodes, each designed for specific applications.

The O.R. Electrode is engineered to answer the special needs of short term monitoring—in operating and recovery rooms—wherever electrode performance can't be compromised.

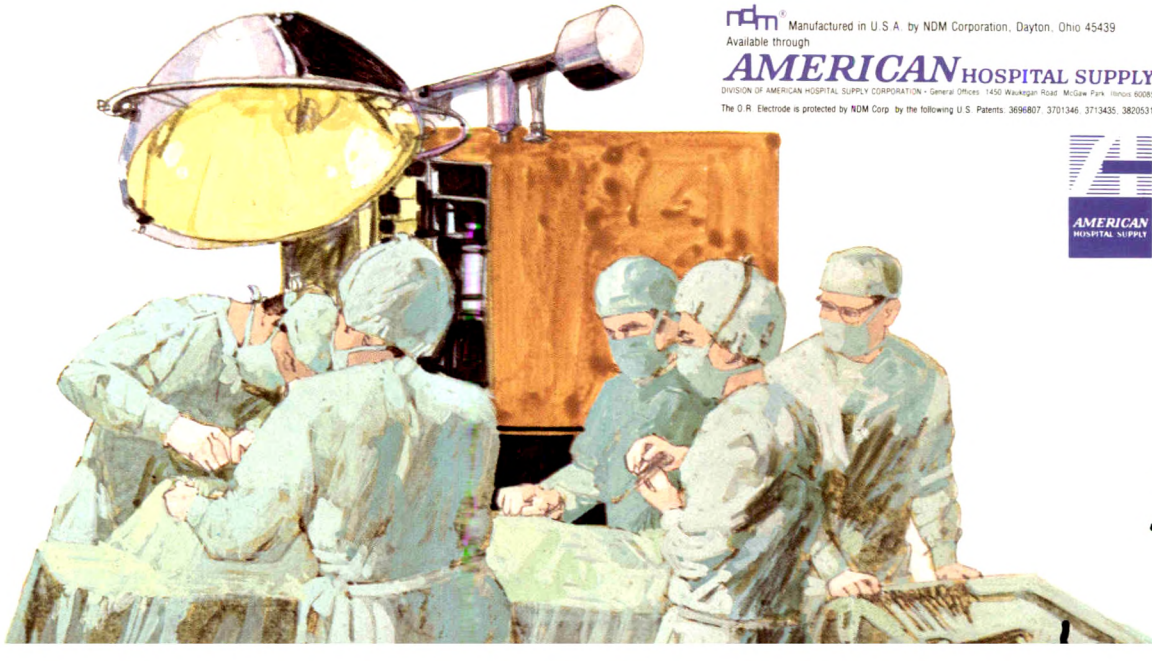
Pregelled and self-adhering, the O.R. Electrode is applied quickly and delivers a strong signal with immediate base line stability.

The gel cup prevents adhesion loss due to gel squeeze out. The mild electrolyte and soft foam construction virtually eliminate patient discomfort.

Best of all, this advanced electrode is fully compatible with your present ECG equipment. With the appropriate American leadwire and cable, you can enjoy the reliability of an electrode system built with one purpose in mind: To bring the highest ECG monitoring performance to your operating and recovery rooms.

A clinical trial will show why American's O.R. Electrode system is the logical choice for your short term monitoring requirements.

Please contact your American Hospital Supply or NDM representative to arrange a no obligation clinical trial, including a total inservice for your staff. American will supply electrodes, leadwires and cables to adapt to your present monitoring units during the trial period.



ndm® Manufactured in U.S.A. by NDM Corporation, Dayton, Ohio 45439

Available through

AMERICAN HOSPITAL SUPPLY

DIVISION OF AMERICAN HOSPITAL SUPPLY CORPORATION • General Offices: 1450 Waukegan Road, McGaw Park, Illinois 60085

The O.R. Electrode is protected by NDM Corp. by the following U.S. Patents: 3696807, 3701346, 3713435, 3820531

AMERICAN HOSPITAL SUPPLY

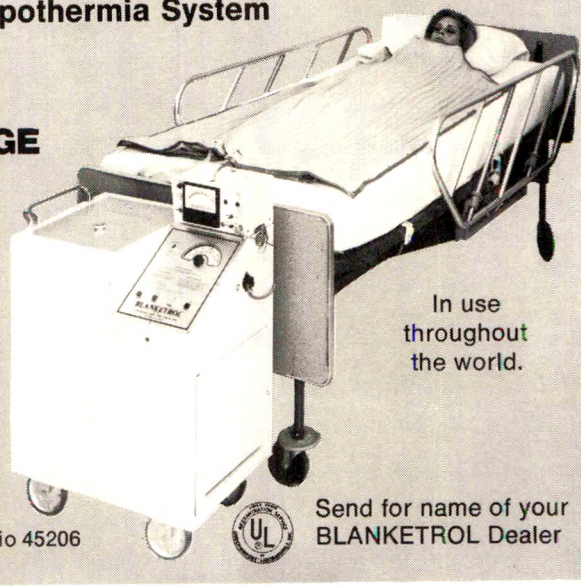
BLANKETROL®

Hyper-Hypothermia System

***SAME* BIG VALUE**

***NEW* SMALL PACKAGE**

Simple two step operation
Accurate and dependable performance
Exclusive safety features
Field serviceable



In use throughout the world.

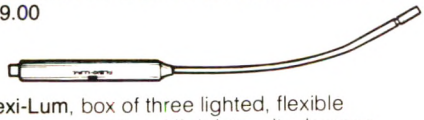
CINCINNATI SUBZERO PRODUCTS INC.
2612 Gilbert Avenue, Cincinnati, Ohio 45206

Send for name of your BLANKETROL Dealer

The new standard in patient care

Prism Laryngoscope, designed to simplify difficult intubations. Enables insertion of an endotrocheal tube with an unobstructed line of vision. Packaged sterile and complete with reusable light.

Cat. No. 9041 includes sterile prism Laryngoscope and Laryngolite, Pack/3 $15.50
Cat. No. 9040 Laryngoscope blades only, sterile, Box/10 $29.50
Cat. No. 1022 Laryngolite, designed to provide illumination for Cat. No. 9040, sterile, Box/10 $29.00



Flexi-Lum, box of three lighted, flexible intubation stylettes. High intensity, laryngoscope bulb on tip of 10" flexible shaft. Two long-lasting AA alkaline batteries with on-off backswitch. Reliable, non-flickering performance until batteries are depleted. Excellent for intubation guidelight, emergency anesthesia light or blind intubation procedures.
Cat. No. 3034, 10" flexible shaft, Pack/3 $31.02

Laryngeal mirror attachment for 006 penlight. Use for viewing posterior pharynx and larynx when anesthetizing prior to bronchoscopy. Packaged 10 per box.
Cat. No. 1506
1-11 boxes $4.25 each
12 + boxes $4.00 each

Tongue Clamp, patented self-locking ratchet with quick thumb release. Excellent for "grabbing" and holding tongue forward in either emergency or routine anesthesia use. Disposable.

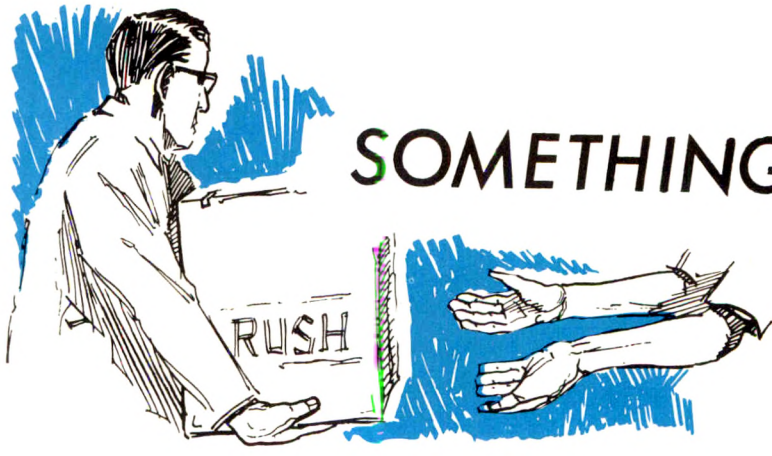
Cat. No. 9000, Box/150 $15.75

Doctor's Six Pak, high-intensity, non-flickering beam, six lights per pack. Batteries not replaceable.
Cat. No. 1006
1-2 Six Paks, $7.00 each
3-5 Six Paks, $6.50 each
6 + Six Paks, $6.00 each

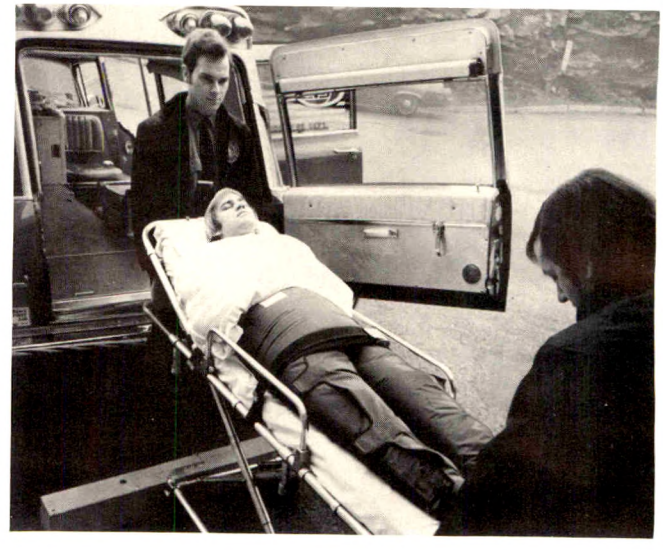
concept INC. **We put ideas to work.**
12707 U.S. Highway 19 South
Clearwater, Florida 33516

If not available from your dealer, order direct from Concept, Inc.

Florida residents add 4% sales tax.



David Clark Company, Medical Products Division, have a new medical anti-shock trouser for pre-hospital trauma treatment. Application of external circumferential pressure results in the autotransfusion of pooled venous blood from below the diaphragm, and, it is claimed, reduces the volume returned to the lower extremities.



★ ★ ★

A new fully automatic clinical blood pressure machine with digital readouts for blood pressure and heart rate has been developed by Med Data, Inc., Madison, Wisconsin.

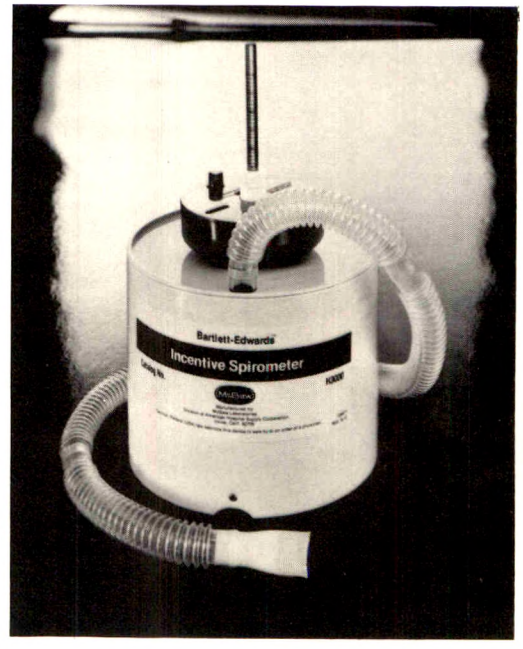
Designated the MDI-410, the device is stated to have the accuracy of 3 millimeters of mercury, and can be operated in a manual or automatic cycle mode. Both digital and analog outputs are available for connection to a computer or chart recorder for data logging.

A unique electronic circuit simulates the threshold discrimination capabilities of the human ear. The sounds are detected in the cuff around the subject's arm, by a special microphone, and sent to electronic circuits for processing. A small computer analyzes the sounds and the time between them to verify that they are truly Korotkoff sounds.

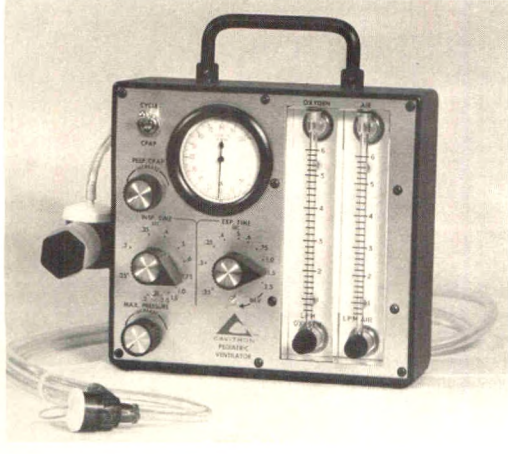
The Bartlett-Edwards Incentive Spirometer, designed to encourage voluntary sustained maximal inspiration, is now available from McGaw Laboratories, Irvine, California.

The Spirometer encourages inhaling to the maximum lung volume without the swallowing of air. Also, the airway/pleural pressure gradients favor complete alveolar inflation.

Patient discomfort is minimal and cardiac output is not decreased. The patient's number of inspirations is recorded automatically on the unit's indicator.



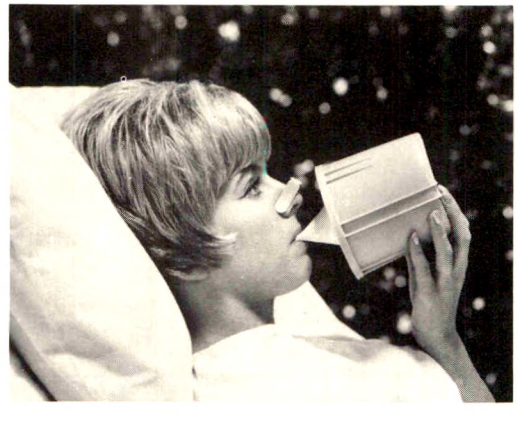
★ ★ ★

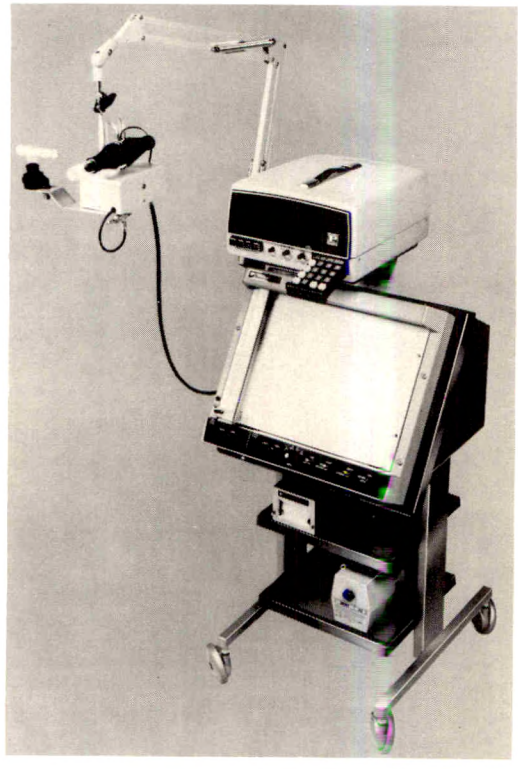


Cavitron/KDC Medical Sales, Anaheim, California, announces the development of their new Cavitron PV-10 Neonatal/Pediatric Transport Ventilator offering convenience and simplicity of operation (only 7 controls), as well as all functions necessary to furnish complete respiratory support for the neonatal/pediatric patient, including IMV, PEEP, CPAP, COAD, and IPPB. Calibrated inspiratory and expiratory time controls facilitate the use of a broad range of I:E ratios, and variable flow rates further facilitate their application.

★ ★ ★

Gaymar Industries, Orchard Park, New York, present The Adler Rebreather, which stimulates deep breathing, by increasing the respiratory tract dead space, causing temporary increase in blood CO_2 when used for 3-5 minutes each hour. It utilizes the established principle of a 1,000 ml dead space incorporated into a compact easily handled unit.





Puritan-Bennett Corporation announces availability of REMAC,® a new portable micro-computerized lung function testing system.

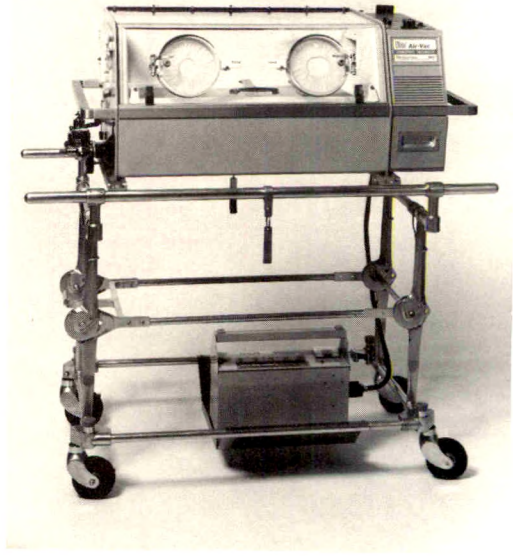
It is claimed that REMAC instantly and accurately senses, computes and displays test results for more than ten commonly measured pulmonary function parameters (including nitrogen washout, flow volume loops and MVV) and may be expanded to measure future additional parameters.

★ ★ ★

Ohio Medical Products, Madison, Wisconsin, has available the AIR-VAC Transport Incubator—a self-sustaining incubator capable of providing intensive care transportation for the premature and critically-ill newborn. One of the primary requirements of the transport incubator is the ability to convey an infant in complete safety under what mode of transportation is necessitated —air, helicopter, or ambulance.

The AIR-VAC Transport Incubator meets the requirements of the Safe Current Limits Standard of the Association for the Advancement of Medical Instrumentation in regard to leakage current.

The AIR-VAC Transport Incubator is capable of operating from any one of four sources of electrical power: 12 Volt DC (automotive), 24 Volt DC (aircraft), 120 Volt AC 50-400 Hz (wall outlet, helicopter or aircraft) or its own 12 Volt DC Battery Pak. (A model designed for 220/240 Volt, 50-400 Hz is available for foreign markets.) Heat is thermostatically controlled, and filtered air is humidified to the 40-60% comfort range from the humidity reservoir with disposable sponge.



The MONOJECT Sterile "Mini" Continuous Epidural Anesthesia Kit from Sherwood Medical Industries, St. Louis, Missouri, features the MONOJECT Hustead Needle with a point designed to accurately direct the catheter into the epidural space.

The new MONOJECT kit includes a radiopaque Teflon catheter with an exclusive luer lock tube connector to replace the blunt needle usually used to link the catheter to the syringe containing anesthetic. The connector eliminates splitting of the catheter that sometimes occurs with a blunt needle, and has a clear hub to allow an aspiration test for blood to assure correct catheter placement.

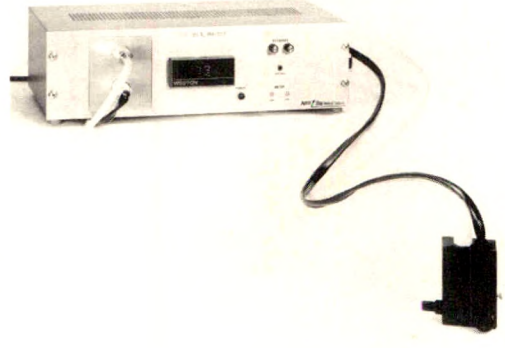
The catheter has five cm graduations from the distal end, and the tip is marked with a zero to give the user a positive check for complete catheter removal. The cap from the luer lock tip connector serves as a luer lock plug in continuous administration procedures.

★ ★ ★

Ohio Medical Products, Madison, Wisconsin, has introduced the Model 720 Nitrogen Gas Analyzer with a specially designed remote sample head.

This new Ohio pulmonary function instrument incorporates a miniaturized gas spectrometer with computer-type linearization circuits to provide usable output signals. An illuminated digital display provides the operator with direct readout of nitrogen concentration to one decimal place with a readout accuracy of 0.1%.

The remote sample head, which is placed near the patient's mouth, continuously draws samples of gas entering and leaving the patient's mouth. Minimum dead space and maximum structural solidarity assure rapid response and repeatable test results. Absolute linearity over an operating range of nitrogen concentration from 2% to 85% is provided through specially designed circuitry in the solid state electronics.



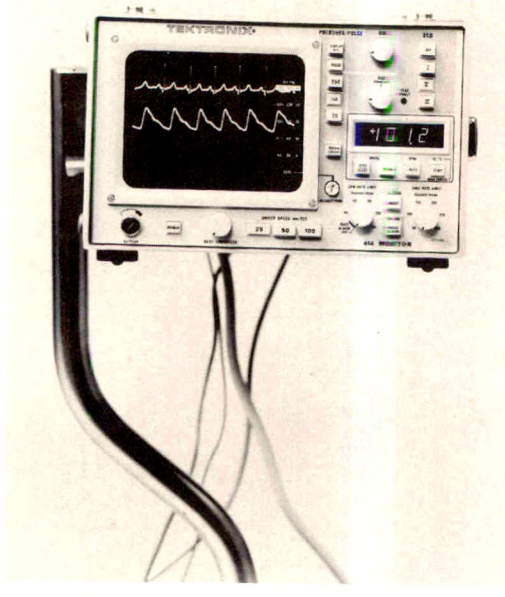
★ ★ ★

The report, "Development and Evaluation of Methods for the Elimination of Waste Anesthetic Gases and Vapors in Hospitals," outlines effective control procedures for eliminating waste anesthetic gases in operating rooms.

This publication, GPO Stock Number 017-033-00071, is available from the Superintendent of Documents, US Government Printing Office, Washington DC 20402. The cost is $2.15 each.

Robertshaw Controls Company, Anaheim, California, announces a new flow selector valve with certain advantages over the commonly used flow meter. It does not have to be mounted vertically but will function accurately in any position. Any of the five flow selections can be dialed easily and quickly.

★ ★ ★



Tektronix®, Beaverton, Oregon, has a new 414 portable patient monitor, featuring digital display of heart rate, systolic/diastolic blood pressures, mean blood pressure and temperature, which increases the monitoring capability of anesthesiologists in the operating room and recovery room. The 414 also gives dual-trace crt display of ECG and blood pressure or peripheral pulse.

Since it can measure mean, as well as arterial, venous, and pulmonary wedge pressures, the 414 adds more complex applications, such as cardiac catheterization, to the realm of portable monitors. Digital readout enhances both accuracy and convenience of measurements.

It also features pulse pressure and heart rate alarms, selectable pressure ranges and sweep speeds, and internal battery pack for cordless operation.

PRECISE, ECONOMICAL, SAFE...

RALS POWER UNIT

...INSTANT ATOMIZATION FOR FAST TOPICAL ANESTHESIA

Fast, measured topical anesthesia is ready at your finger tips in a Rals Power Unit. Forget about pumping bulbs, uneven atomization, and limited spraying duration. The Rals Power Unit uses a non-toxic propellant, dichlorodifluoromethane (freon) to activate standard DeVilbiss Atomizers No's. 151, 152 and 163. Instantly, a fine mistlike spray is produced. A graduated solution vial is available for measuring the amount of solution administered.

The Rals Power Unit has been proven effective in cocainization prior to endotracheal intubation, endoscopic instrumentation, laryngotracheal insufflation, and in a variety of nose and throat procedures.

Rals Power Unit #168 are supplied six to a box with adaptor top and metal base. Illustration shows #152 atomizer. All styles in stock.

WRITE OR PHONE FOR LITERATURE, PRICE LIST.

RALS LABORATORIES DIVISION
SCHUEMANN Laboratories, Inc.
480 WEST AURORA ROAD • NORTHFIELD, OHIO 44067

SL-45

I. A. R. S.

50th CONGRESS

MARCH 14-18, 1976

CAESARS PALACE
LAS VEGAS, NEVADA

Get the Anesthesia Spirit of '76

Plan Now to Attend

212-978-6900 516-546-5511
800-645-2059

MEDICAL MANAGEMENT CO.

A National Organization — Established 1946

COLLECTIONS • DATA PROCESSING • MANAGEMENT •

All Third Party Claims Processed

Home Office
76 Pine Street Freeport, N.Y. 11520

Classified Advertising

PEDIATRIC ANESTHESIOLOGY RESIDENCY

Childrens Hospital of Los Angeles

Three-phase program: Clinical, Academic, Investigative, emphasizing practical aspects of anesthesiology related to infants and children.

AMA approval for third-year residency. Positions available from two months to one year.

Apply: George B. Lewis, Jr., M.D.
Head, Division of Anesthesiology
Childrens Hospital of Los Angeles
4650 Sunset Boulevard
Los Angeles, California 90054
Phone (213) 660-2450, Ext. 2262

APPROVED THREE-YEAR ANESTHESIOLOGY RESIDENCY

Available July 1, 1976, in 620-bed, active general hospital, pain clinic, over 12,000 anesthetic procedures annually. Training in all phases of anesthesiology and resuscitation including modern recovery unit, acute cardiopulmonary medicine, computer sciences (if requested) and clinical research, coronary care, intensive care facility and neonatal unit. Special emphasis placed upon regional and conduction anesthesia. First year annual stipend $9,450 plus maintenance and modern apartments close to hospital. Apply for further particulars to: P. C. Lund, M.D., Director, Department of Anesthesiology, Conemaugh Valley Memorial Hospital, Johnstown, Pennsylvania 15905.

ANESTHESIOLOGY—66-man medical group located next to modern, accredited 480-bed hospital seeks Board Certified anesthesiologist to join two associates. Located in upper midwest university metropolitan area of 105,000; 35 minutes from superb clean lake region; associated with four-year medical school, teaching opportunities available; salary open; all specialties represented; will pay travel expenses for physician and spouse for interview. Write Box 11-75-A in care of I.A.R.S.

FACULTY POSITIONS

Department of Anesthesiology, Charity Hospital, New Orleans, affiliated with LSU and Tulane Medical Schools, has three faculty positions open for board certified/eligible anesthesiologists at Associate-Assistant Professor, Instructor levels. Duties involve teaching, research, clinical supervision. Salaries negotiable. Send inquiries and curriculum vitae to: M. Naraghi, M.D., Director, Department of Anesthesiology, Charity Hospital, New Orleans, Louisiana 70140.

CARDIAC ANESTHESIOLOGY FELLOWSHIP

Applications are invited for the period of July 1976 to June 1977 as a third year of anesthesiology training at the Health Center of the University of Pittsburgh. The successful applicant will become a team member in the provision of anesthesia and life support for patients undergoing open heart surgery and will have ample opportunity to pursue research interests at the clinical and laboratory level. For further details apply to:

Malcolm D. Orr, M.B., B.S., Ph.D.
Director of Cardiovascular Anesthesia
Department of Anesthesiology and Critical Care Medicine
University of Pittsburgh
Pittsburgh, Pennsylvania 15213

CHIEF OF ANESTHESIA—Opportunity for developing exclusive anesthesia group services and educational programs for 480-bed JCAH hospital with teaching program and university affils. In West Georgia city of 250,000 approx. 90 miles near Atlanta. Arrangements negotiable. Write Box 11-75-B in care of I.A.R.S.

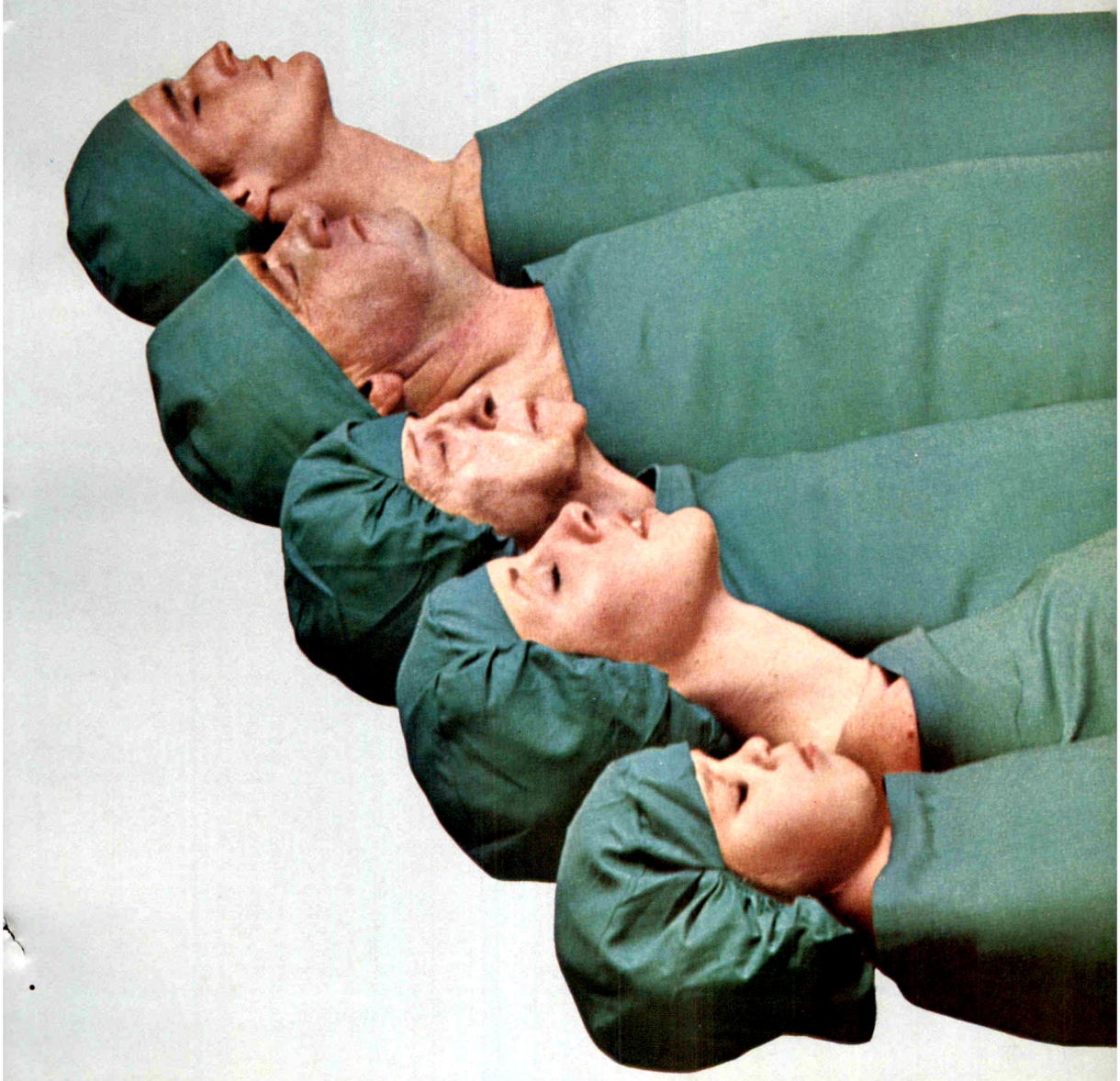
WANTED IMMEDIATELY — Full-time and part-time Anesthesiologists for positions at small private hospital in Queens, N.Y. Salary competitive. Contact Box 11-75-C in care of I.A.R.S.

Rates for classified advertising are $3.00 per line, minimum 5 lines. Box number ads $3.50 per line. Classified Display rates on request. Copy deadline 6 weeks prior to publication. Do not submit payment with order; invoices will be sent for payment prior to publication. Ad copy, subject to acceptance by publisher, should be mailed to: Anesthesia and Analgesia . . . Current Researches, 3645 Warrensville Center Rd., Cleveland, Ohio 44122.

Clinically proven
nondepolarizing muscle relaxant

PAVULON®
pancuronium bromide

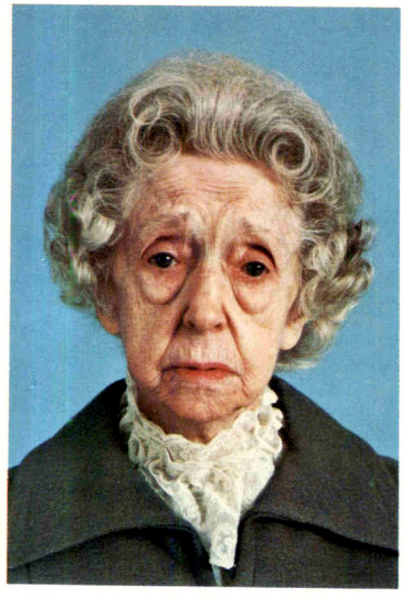
for many patients
for many reasons

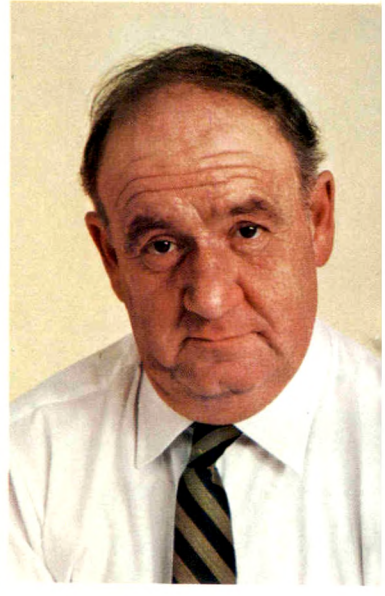


Please turn page for full prescribing information

An unusually fast-acting nondepolarizing blocking agent [1-5]

PAVULON®
pancuronium bromide





for many patients for many reasons

in pediatric surgery[6-12]

Pavulon® has been used with satisfactory results in pediatric patients undergoing elective surgery[11], abdominal surgery[7] and cardiovascular surgery[8]. Dose response studies indicate that, except for neonates, dosage is the same as for adults. In neonates, a test dose of 0.02 mg/kg is recommended to determine responsiveness.

in geriatric surgery[13]

Pavulon® can be considered a preferred relaxant for major surgical procedures in the aged patient because of the relative absence of significant side effects.

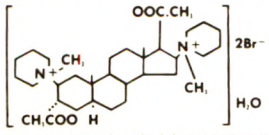
in the high risk patient[2-5, 14-18]

Pavulon® is often preferred for poor risk patients[5,14,16] especially those with asthma or chronic bronchitis[2,14,16,17], cardiovascular disease[4,5,16,18] and patients undergoing abdominal, thoracic or other major surgery[2,5], including open heart surgery[15]. Caution should be exercised, however, in the presence of renal disease since a major portion of the administered drug is excreted unchanged in the urine.

PAVULON® (pancuronium bromide)

THIS DRUG SHOULD ONLY BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: Pavulon (pancuronium bromide) is the aminosteroid 2 beta, 16 beta-dipiperidine-5 alpha-androstane-3 alpha, 17 beta-diol diacetate dimethobromide. It has the following structural formula:



ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon is approximately 5 times as potent as d-tubocurarine chloride.

The onset and duration of action of Pavulon is dose dependent. With the administration of 0.04 mg. per kg. the onset of action, as measured by a peripheral nerve stimulator, is usually within 45 seconds, and its peak effect is usually within 4½ minutes; recovery to 90% of control twitch height usually takes place in less than one hour. Larger doses, more suitable for endotracheal intubation, such as 0.08 mg. per kg. of Pavulon have an onset of action of about 30 seconds, and a peak effect within 3 minutes. Supplemental incremental doses of Pavulon, following the initial dose, slightly increase the magnitude of blockade, and significantly increase the duration of the blockade.

Pavulon has little effect upon the circulatory system. The most frequently reported observation is a slight rise in pulse rate.

Human histamine assays, and clinical observations, as well as in *vivo* guinea pig testing, and in *vitro* mast cell testing, indicate that histamine release rarely, if ever, occurs.

Pavulon is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, kanamycin, and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

Pavulon has no known effect on consciousness, the pain threshold, or cerebration.

INDICATIONS: Pavulon is indicated as an adjunct to anesthesia to induce skeletal muscle relaxation. It may also be employed to facilitate the management of patients undergoing mechanical ventilation.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards. There are insufficient data to support safe use of Pavulon in obstetrics, so such use is not recommended.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: The most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane, and methoxyflurane. No increase in intensity of blockade or duration of action of Pavulon is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. The dosage information which follows has been derived from dose-response studies based on body weight and is intended to serve as a guide only. Since potent inhalational agents or prior administration of succinylcholine enhance the intensity of blockade and duration of Pavulon (see DRUG INTERACTION), these factors should be taken into consideration in selection of initial and incremental dosage.

In adults the initial intravenous dosage range is 0.04 to 0.1 mg. per kg. Later incremental doses starting at 0.01 mg. per kg. may be used. These increments slightly increase the magnitude of the blockade, and significantly increase the duration of blockade, because a significant number of myoneural junctions are still blocked when there is clinical need for more drug.

If Pavulon is used to provide skeletal muscle relaxation for endotracheal intubation, doses of 0.06 to 0.1 mg. per kg. are recommended. Conditions satisfactory for intubation are usually present within 2 to 3 minutes. The ability of the anesthetist to intubate with Pavulon (pancuronium bromide) improves with experience.

Dosage in Children: Dose-response studies in children indicate that, with the exception of neonates, dosage requirements are the same as for adults. Neonates are especially sensitive to nondepolarizing neuromuscular blocking agents, such as Pavulon, during the first month of life. It is recommended that a test dose of 0.02 mg. per kg. be given first in this group to measure responsiveness.

MANAGEMENT OF PROLONGED NEUROMUSCULAR BLOCKADE: Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Pavulon as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade. Under such circumstances the primary treatment is manual or mechanical ventilation and maintenance of a patent airway until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) or neostigmine, in conjunction with atropine, will usually antagonize the skeletal muscle relaxant action of Pavulon. These should be accompanied by or preceded by injection of atropine sulfate to minimize the incidence of cholinergic side effects, notably excessive secretions and bradycardia. Satisfactory reversal can be judged by adequacy of skeletal muscle tone, and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and adjuncts which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade; ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference to the specific package insert of the reversal agents should be made.

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED:

2 ml. ampuls—2 mg./ml.—box of 25
5 ml. ampuls—2 mg./ml.—box of 25
10 ml. multiple dose vials—1 mg./ml.—box of 25

References:

1. Baird, W. L. M. and Reid, A. M.: Brit. J. Anaesth. *39*:775, 1967.
2. McDowell, S.A. and Clarke, R.S.J.: Anaesthesia *24*:581, 1969.
3. Katz, R. L.: Anesthesiology *34*:550, 1971.
4. McIntyre, J. W. R. and Gain, E. A.: Anesth. and Analg. *50*:813, 1971.
5. Dobkin, A.B., *et al.*: Canad. Anaesth. Soc. J.: *18*:512, 1971.
6. Nightingale, D. A. and Bush, G. H.: Brit. J. Anaesth. *45*:63, 1973.
7. Goudsouzian, N. C., Ryan, J. F., and Savarese, J. J.: Anesth. *41*:95, 1974.
8. Bennett, E. J., Dalal, F. Y., and Fisher, M.: M. E. J. Anaesth. *3*:413, 1972.
9. Yamamoto, T., Baba, H., and Shiratsuchi, T.: Anesth. and Analg. *51*:919, 1972.
10. Bennett, E. J., Bowyer, D. E., Giesecke, Jr., A. H., and Stephen, C. R.: Anesth. and Analg. *52*:12, 1973.
11. Lippmann, M. and Rogoff, R. C.: Anesth. and Analg. *53*:684, 1974.
12. Bennett, E. J., Daughety, M. J., Bowyer, D. E., and Stephen, C. R.: Anesth. and Analg. *50*:798, 1971.
13. Lorhan, P. H. and Lippmann, M.: Anesth. and Analg. *51*:914, 1972
14. Fastner, Z. and Agoston, S.: Clinical Trials J. 7:254, 1970.
15. Sellick, B. A.: Der Anaesthesist *20*:76, 1971.
16. Baird, W. L. M.: Irish J. Med. Sc. (7th Series) *1*:559, 1968.
17. Nana, A., Cardan, E., and Leitersdorfer, T.: Anaesthesia *27*:154, 1972.
18. Levin, N. and Dillon, J.B.: Anesth. and Analg. *50*:808, 1971.

Organon

Organon Inc.
West Orange, N. J. 07052

The tender touch

These soft, pliable blood pressure cuffs are ideal for use on newborns and infants. Incorporating a Latex bladder, minimizing any chances for skin irritation, and Silicon wrap-around with 12-inch inflating tube. They are secured by the Velcro hook and pile method, with no eyes to hook nor ends to tuck in. They are instantly peeled apart for easy removal.

Cuffs are available in two sizes:
22080 - 1⅜ x 5" (new born)
22081 - 2¼ x 6" (infant)

For additional information write for brochure number 27.

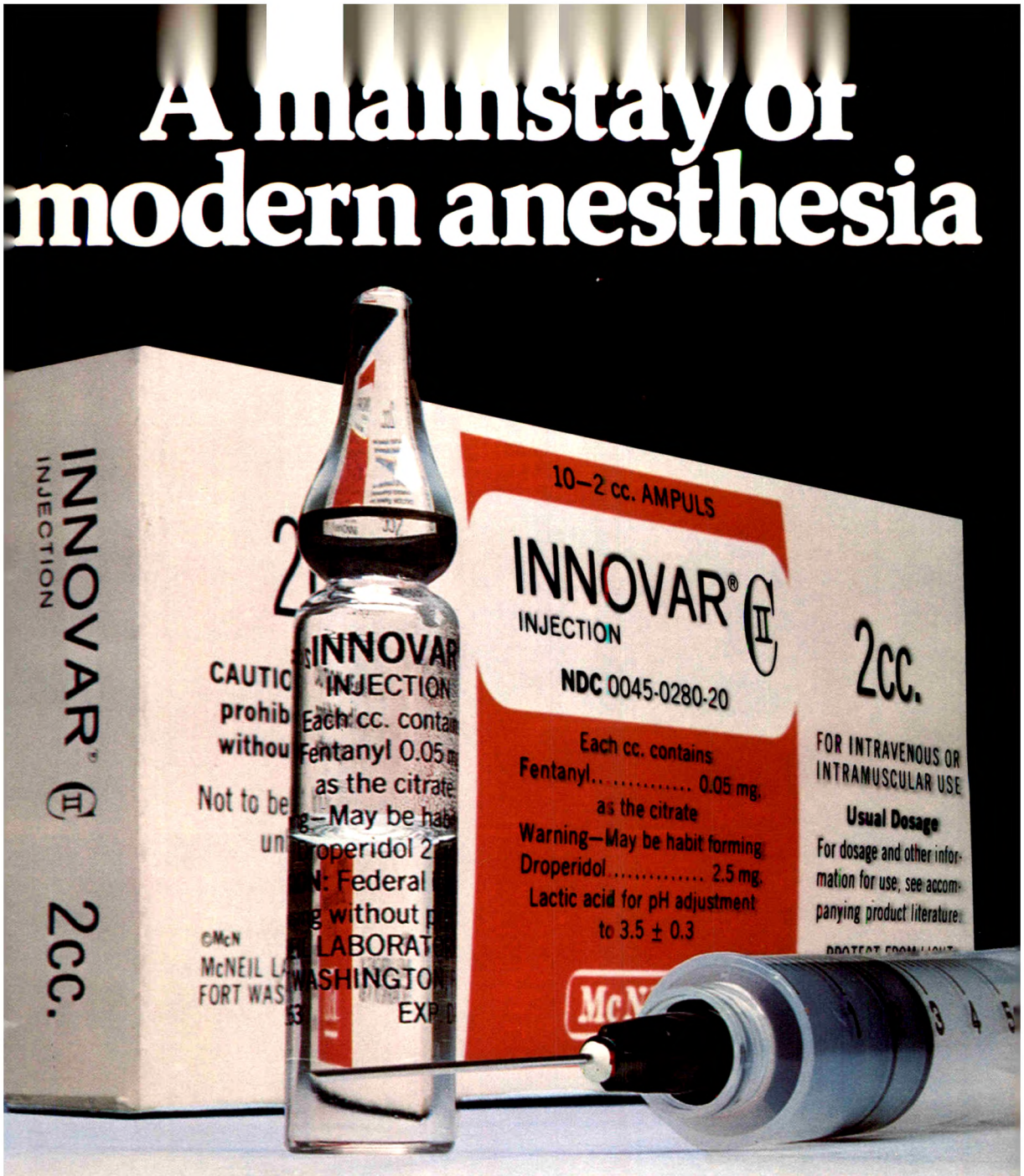
DUPACO
INCORPORATED
P.O. Box 98,
San Marcos, CA 92069

TO ASSURE THAT YOU WILL CONTINUE
TO RECEIVE YOUR COPY OF

ANESTHESIA & ANALGESIA
. . . Current Researches

WITHOUT INTERRUPTION, PLEASE NOTIFY
THE BUSINESS OFFICE AS FAR IN ADVANCE
AS POSSIBLE OF ANY CHANGE IN ADDRESS.

A mainstay of modern anesthesia



- As an adjunct to general anesthesia
- As a supplement to regional anesthesia
- Used without a general anesthetic in certain diagnostic procedures

INNOVAR® injection is available for use only upon direction of a physician.

Special educational material available

A Programmed Instruction Manual on the chemistry, pharmacology and clinical applications of INNOVAR injection and its components is available from McNeil Laboratories. For further information, please write: Medical Dept., McNeil Laboratories, Inc., Fort Washington, Pa. 19034, Attn: Robert T. McSherry, M.D.

© McN 1975

For prescribing information including Contraindications, Warnings, Precautions and Adverse Reactions, please turn page.

Innovar® injection (C)

The two components of INNOVAR® injection, fentanyl and droperidol, have different pharmacologic actions. Before administering INNOVAR injection, the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action.

DESCRIPTION

Each cc. contains (in a 1:50 ratio):

Fentanyl ..... 0.05 mg.
as the citrate

Warning: May be habit forming

Droperidol ..... 2.5 mg.
Lactic acid for adjustment of pH to 3.5± 0.3

FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY

Protect from Light

ACTIONS INNOVAR injection is a combination drug containing a narcotic analgesic, fentanyl, and a neuroleptic (major tranquilizer), droperidol. The combined effect, sometimes referred to as neuroleptanalgesia, is characterized by general quiescence, reduced motor activity, and profound analgesia; complete loss of consciousness usually does not occur from use of INNOVAR injection alone. The incidence of early postoperative pain and emesis may be reduced.

A. Fentanyl is a narcotic analgesic with actions qualitatively similar to those of morphine and meperidine. Fentanyl in a dose of 0.1 mg. (2.0 cc.) is approximately equivalent in analgesic activity to 10 mg. of morphine or 75 mg. of meperidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. Fentanyl appears to have less emetic activity than other narcotic analgesics. Histamine assays, and skin wheal testing in man, as well as *in vivo* testing in dogs indicate that histamine release rarely occurs with fentanyl.

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. It may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia, and bronchoconstriction.

The onset of action of fentanyl is almost immediate when the drug is given intravenously; however, maximal analgesic and respiratory depressant effect may not be noted for several minutes. The average duration of action of the analgesic effect is 30 to 60 minutes. Following intramuscular administration, the onset of action is from seven to eight minutes, and the duration of action is from one to two hours. Although the duration of the respiratory depressant effect is unknown, as with other narcotic analgesics, it may be considerably longer than the analgesic effect.

B. Droperidol produces marked tranquilization and sedation. It also produces an antiemetic effect as evidenced by the antagonism of apomorphine in dogs. It potentiates other CNS depressants. It also produces mild alpha adrenergic blockade, peripheral vascular dilatation and reduction of the pressor effect of epinephrine. Droperidol can produce hypotension and decreased peripheral vascular resistance. It may decrease pulmonary arterial pressure (particularly if it is abnormally high). It may reduce the incidence of epinephrine-induced arrhythmias but it does not prevent other cardiac arrhythmias. The onset of action is from three to ten minutes following intravenous or intramuscular administration. The full effect, however, may not be apparent for 30 minutes. The duration of the sedative and tranquilizing effects generally is two to four hours. Alteration of consciousness may persist as long as 12 hours. This is in contrast to the much shorter duration of action of fentanyl.

INDICATIONS INNOVAR injection is indicated to produce tranquilization and analgesia for surgical and diagnostic procedures. It may be used as an anesthetic premedication, for the induction of anesthesia, and as an adjunct in the maintenance of general and regional anesthesia. If the supplementation of analgesia is necessary, SUBLIMAZE® (fentanyl) injection alone rather than the combination drug INNOVAR injection should usually be used.

CONTRAINDICATIONS INNOVAR injection should not be used in patients who are hypersensitive to either component.

WARNINGS PATIENTS WHO HAVE RECEIVED *INNOVAR* INJECTION SHOULD BE UNDER APPROPRIATE SURVEILLANCE.

RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INNOVAR injection, the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses, as low as 1/4 to 1/3 those usually recommended.

INNOVAR injection may cause muscle rigidity, particularly involving the muscles of respiration. This effect is due to the fentanyl component and is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs it is managed by the use of assisted or controlled respiration and by a neuromuscular blocking drug, if necessary.

FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD ALSO BE AVAILABLE.

Drug Dependence: *Fentanyl, the narcotic analgesic component, can produce drug dependence of the morphine type and therefore has the potential for being abused.*

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl, in this regard, has not been established, the use of INNOVAR injection or SUBLIMAZE fentanyl in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure: INNOVAR injection should be used with caution in patients who may be particularly susceptible to respiratory depression such as comatose patients who may have a head injury or brain tumor. In addition, these drugs may obscure the clinical course of patients with head injury.

Usage in Children: The safety of INNOVAR injection in children two years of age or younger has not been established.

Usage in Pregnancy: The safe use of INNOVAR injection has not bee established with respect to possible adverse effects upon fetal developmen

Therefore, it should be used in women of childbearing potential only when, in tl judgment of the physician, the potential benefits outweigh the possible hazard There are insufficient data regarding placental transfer and fetal effect therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS *The initial dose of INNOVAR injection should be appropri ly reduced in elderly, debilitated and other poor risk patients. The effect of t initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal anesthesia and sor peridural anesthetics, can alter respiration by blocking intercostal nerves, and c cause peripheral vasodilatation and hypotension because of sympathet blockade. Through other mechanisms (see Actions) fentanyl and droperidol al depress respiration and blood pressure. Therefore, when INNOVAR injection used to supplement these forms of anesthesia, the anesthetist must be famili with the physiological alterations involved, and be prepared to manage them the patients selected for this form of anesthesia.

The droperidol component of INNOVAR injection may decrease pulmonar arterial pressure. This fact should be considered by those who conduct diagnost or surgical procedures where interpretation of pulmonary arterial pressu measurements might determine final management of the patient.

Vital signs should be monitored routinely.

INNOVAR injection, and SUBLIMAZE fentanyl, should be used with cautio in patients with chronic obstructive pulmonary disease, patients with decrease respiratory reserve, and others with potentially compromised ventilation. In suc patients narcotics may additionally decrease respiratory drive and increa airway resistance. During anesthesia this can be managed by assisted c controlled respiration. Postoperatively respiratory depression caused b narcotic analgesics can be reversed by narcotic antagonists (levallorphar nalorphine, and naloxone); consult individual prescribing information befo using.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, an general anesthetics) have additive or potentiating effects with INNOVA injection. When patients have received such drugs, the dose of INNOVA injection required will be less than usual. Likewise, following the administratio of INNOVAR injection the dose of other CNS depressant drugs should b reduced.

INNOVAR injection should be administered with caution to patients with live and kidney dysfunction because of the importance of these organs in th metabolism and excretion of drugs.

If hypotension occurs, the possibility of hypovolemia should be considered an managed with appropriate parenteral fluid therapy. Repositioning the patient t improve venous return to the heart should be considered when operativ conditions permit. It should be noted that in spinal and peridural anesthesia tilting the patient into a head down position may result in a higher level o anesthesia than is desirable, as well as impair venous return to the heart. Car should be exercised in the moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus these other countermeasures do not correct the hypotension, then the administration o pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INNOVAR injection due to the alpha-adrenergic blocking action of droperidol.

The fentanyl component may produce bradycardia, which may be treated with atropine; however, INNOVAR injection should be used with caution in patients with cardiac bradyarrhythmias.

When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

ADVERSE REACTIONS The most common serious adverse reactions reporte to occur with INNOVAR injection are respiratory depression, apnea, muscular rigidity, and hypotension; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have beer observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, twitching, blurred vision, hyperactivity on induction, laryngospasm, transient hypertension, nausea and emesis, diaphoresis, emergence delirium, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).

Postoperative drowsiness is also frequently reported.

OVERDOSAGE ***Manifestations:*** The manifestations of INNOVAR injection overdosage are an extension of its pharmacologic actions.

Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered. A specific narcotic antagonist such as nalorphine, levallorphan or naloxone should be available for use as indicated to manage respiratory depression caused by the narcotic component fentanyl. This does not preclude the use of more immediate countermeasures. Consult the package inserts for the individual narcotic antagonists for details about use.

HOW SUPPLIED INNOVAR® injection is supplied in 2 cc. (**NDC** 0045-0280-20) and 5 cc. (**NDC** 0045-0280-50) ampuls, in packages of 10.

IMPORTANT: Complete dosage information is available in insert which accom panies each package (or on request). The drug is available only upon direction of a physician.

U.S. Patent No. 3,141,823

9774

McNEIL **McNeil Laboratories, Inc.**
Fort Washington, Pa. 19034

INDEX OF ADVERTISERS

Air Products and Chemicals, Inc. (19), (20), (21), (22), (23), (24)
Air Products and Chemicals, Inc.—*Laryngoscope Blades* (72)
Allergan Pharmaceuticals—*Lacri-Lube*® (49)
American Optical, Medical Division—*Fiber Optic Laryngoscope* (6), (7)
Applied Medical Research Corporation—*Blood Pressure Monitor* (45)
Ayerst Laboratories—*Fluothane*® (10), (11), (12)
Burroughs Wellcome Co.—*Anectine*® (16), (17)
Cincinnati Sub-Zero Products, Inc.—*Blanketrol*® (55)
Concept, Inc.—*Anesthesia Products* (55)
Diamed Division, Illinois Tool Works—
An·Trol(TM) *Anesthesia Circle System* (36)
Dupaco, Inc.—*Anesthesia Apparatus* (37)
Dupaco, Inc.—*Blood Pressure Cuffs* (66)
J. H. Emerson Company—*IMV Ventilator* (13)
Halocarbon Laboratories, Inc.—*Halothane Gas* (70), (71)
Harris-Lake, Inc.—*Mark 14 Wright Respirometer* (2)
McNeil Laboratories, Inc.—*Innovar*® (67), (68)
McNeil Laboratories, Inc.—*Sublimaze*® (26), (27), (28)
Medical and Industrial Equipment Div., Claudius Ash, Inc.—
Jackson-Rees T-Piece (15)
Medical Management Company—*Management Services* (61)
Medsonics, Inc.—*Versatone*(TM) *Doppler* (33)
National Catheter Corp.—*Catheters* (8), (9)
NDM Corporation—*Grounding Pad and O.R. Electrode System* (53), (54)
North American Drager—*Anesthesia Products* (29)
Ohio Medical Products—*Disposable Anesthesia Circuits* (38), (39)
Ohio Medical Products—*Disposable Endotracheal Tubes* (14)
Ohio Medical Products—*Ethrane*® (46), (47), (48)
O'Neal, Jones & Feldman, Inc.—*Antilirium* (30)
Organon, Inc.—*Pavulon*® (63), (64), (65)
Pfizer Laboratories—*Vistaril*® *I.M.* (50), (51), (52)
A. H. Robins Co., Inc.—*Dopram*® (34), (35)
Schuemann Labs (Rals Div.)—*Rals Power Unit* (61)
Tektronix, Inc.—*Portable Patient Monitor* (18)
Winthrop Laboratories—*Talwin*® *Parenteral* (31), (32)

When halothane is the anesthetic of choice...

Now you have a choice of halothanes -

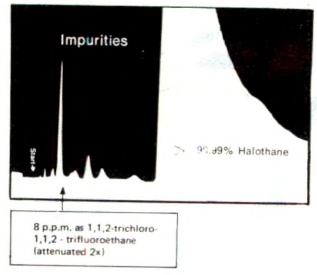
A HIGH PURITY HALOTHANE is now available direct from an experienced producer. For over four years our Canadian subsidiary has been producing and distributing halothane in Canada, Australia, Italy, France, Denmark and elsewhere overseas. For almost two years American military hospitals have been using our halothane, and currently members of many major U.S. hospital purchasing groups have switched to Halocarbon halothane.

Halothane is one of the purest organic compounds made commercially. But a high sensitivity gas chromatograph can draw a graph from which the identity and amount of impurities can be determined. Typical analyses for the Halocarbon and the ICI (Ayerst) products are shown on the right.

Both products are well over 99.99% pure and contain impurities at the ppm level that would be nontoxic at concentrations 10,000 times higher. (1,2)

Our pure product can give you substantial price saving. You may have noticed the drop in the prevailing price last spring when our halothane was first introduced to general use in the United States. Even after that drop our price is about 20% lower. Our consistent high purity plus years of experience in use together give assurance of reliability and your hospital will appreciate our lower prices. So why not ask your pharmacist to request our literature and prices?

I.C.I. (Ayerst) • Halothane • Lot 1 GSM

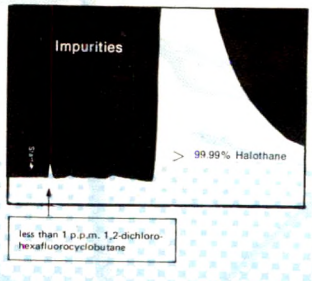


Chromatographic IC Analysis

Analysis Conditions

Sample	Halothane
Injection	50 µl
Column	9 ft. x ¼ in. (2 stage) 1st 6 feet: 30% Carbowax 400 on 60-80 mesh Firebrick Last 3 feet: 30% Dinonyl phthalate on 60-80 mesh Firebrick
Column temp.	50°C
Gas flow	60 ml./min. nitrogen
Injection temp.	100°C
Detector	Flame Ionization
Attenuation	X1 (except as noted)

Halocarbon • Halothane • Lot (L) 17202



(1) Chapman, J., Hill, R., Muir, J., Suckling, C.W., and Viney, D.J., J. Pharm. Pharmac., *19*, 231-39 (1967). This paper from I.C.I.'s laboratory reported typical concentrations of impurities in their halothane of slightly over 22 p.p.m. In our tests we have found impurity levels ranging from very low to 21 p.p.m.

(2) Sherer, O. and Weigand, W., Anaesthesist *13*, 313 (1964). This paper describes the treatment of rats with 4.1% by volume of 1,2-dichlorohexafluorocyclobutane for 2 hours. Anesthesia did not occur and there were no significant pathological findings on examination of the major organs.

HALOCARBON

LABORATORIES, INC.

82 BURLEWS COURT, HACKENSACK, N. J. 07601 201/343-8703

A Word about Insert Language

We doubt that many practitioners are aware of the latest version of the Halothane insert. The insert is a published statement of the generally accepted methods of use. Because it can be revised and because important revisions are done by "blue ribbon" committees of anesthesiologists the insert carries much greater authority than journal articles. And consequently the precise wording of the insert looms very large in malpractice cases.

There has been an important change recently in our insert wording. As a result of a more careful evaluation of halothane data, the following sequence appears in our new insert under Warnings:

When a previous exposure to Halothane U.S.P. was followed by unexplained jaundice, consideration should be given to the use of other anesthetic agents.

Replacing the earlier statement in Contraindications:

Halothane U.S.P. should be avoided when a previous exposure was followed by fever and jaundice, or when there was an unexplained postoperative fever.

This revision makes two fundamental changes in the recommendations regarding exposure to halothane of patients with previous postoperative problems after halothane.

- **It removes "unexplained fever" completely as a contraindication.**
- **It softens considerably the caution against reexposure to halothane when postoperative jaundice followed a previous use.**

Both of these are important changes in a generally accepted statement of prudent practice.

Halothane

U.S.P.

PHYSICAL PROPERTIES OF HALOTHANE

Structure	$CF_3CHBrCl$
Molecular weight	197.4
Boiling Point at 760 mm. of Hg	50.2°C
Specific gravity gas (air=1)	6.8 (calculated)
liquid	1.87
Solubility in 100 parts of water	0.345 parts
Vapor pressure at 20°C	243 mm. of Hg
Blood/gas partition coefficient at 37°C	2.3

DESCRIPTION

Halothane U.S.P. is an inhalation anesthetic which is nonflammable and nonexplosive. When exposed to light this drug decomposes slowly and may form volatile acids. To stabilize the product thymol (0.01% w/w) has been added, and the product packed in colored bottles. Halothane U.S.P. is stable in contact with soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Halothane U.S.P. is soluble in rubber, some plastics, and similar materials; such materials will deteriorate rapidly in contact with Halothane U.S.P. vapor or liquid.

Thymol accumulates in vaporizers because it is much less volatile than Halothane U.S.P., and in time a yellow color may develop in the wick and remaining liquid. Residual thymol can easily be washed out with a small amount of fresh Halothane U.S.P.

ACTIONS

Halothane U.S.P. is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. Halothane U.S.P. progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. Halothane U.S.P. is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

Halothane U.S.P. reduces the blood pressure, and frequently decreases the pulse rate and the greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. Halothane U.S.P. does not cause the release of catecholamines from adrenergic stores. Halothane U.S.P. also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during Halothane U.S.P. anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. Halothane U.S.P. sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. Halothane U.S.P. increases cerebral spinal fluid pressure. Halothane U.S.P. produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. Halothane U.S.P. augments the action of nondepolarizing relaxants and ganglionic blocking agents. Halothane U.S.P. is a potent uterine relaxant.

INDICATIONS

Halothane U.S.P. is indicated for the induction and maintenance of anesthesia.

CONTRAINDICATIONS

Halothane U.S.P. is not recommended for obstetrical anesthesia except when uterine relaxation is required.

WARNINGS

When a previous exposure to Halothane U.S.P. was followed by unexplained jaundice, consideration should be given to the use of other anesthetic agents.

Halothane U.S.P. should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems: otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, i. e. depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

USAGE IN PREGNANCY: Safe use of Halothane U.S.P. has not been established with respect to possible adverse effects upon fetal development. Therefore, Halothane U.S.P. should not be used in women where pregnancy is possible, and particularly during early pregnancy unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

PRECAUTIONS

The uterine relaxation obtained with Halothane U.S.P. unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

Halothane U.S.P. increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if Halothane is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assesed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during Halothane U.S.P. anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by Halothane U.S.P.

ADVERSE REACTIONS

The following adverse reactions have been reported: hepatic necrosis, cardiac arrest, hypotention, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

DOSAGE AND ADMINISTRATION

Halothane U.S.P. may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

HOW SUPPLIED

Amber bottles of 125 ml and 250 ml stabilized with 0.01% (w/w) thymol.

CAUTION: FEDERAL LAW (U. S. A.) PROHIBITS DISPENSING WITHOUT PRESCRIPTION

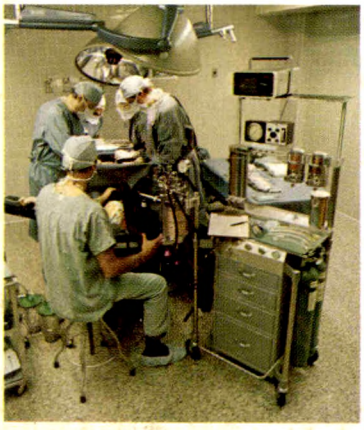
November 1975

HALOCARBON

LABORATORIES, INC.

82 BURLEWS COURT, HACKENSACK, N. J. 07601 201/343-8703

In your hands... the light where you need it.



Light placement. Shaft length. Tip curvature. The largest variety of blade and handle sizes available. Whatever your style preference, there's a Foregger laryngoscope that's just right for you. Choose Miller, MacIntosh, Phillips, Wis-Foregger, Siker, Flagg, Whitehead, Fink, Wis-Hipple, Polio, Guedel, Eversole, Bennett, Bizarri-Guiffrida, or Snow. A full range — each manufactured with quality-designed craftsmanship.

From the routine intubation to the most unusual, Foregger laryngoscope blades help put the light where you need it. For more information, contact your sales representative, Foregger dealer, or write to Air Products and Chemicals, Inc., Medical Products Division, P.O. Box 538, Allentown, Pa. 18105.

Air Products

FOREGGER

Hea.
22.377

Anesthesia AND Analgesia

.....CURRENT RESEARCHES

Factors Influencing Choice Between Tracheostomy and Prolonged Translaryngeal Intubation in Acute Respiratory Failure: A Prospective Study ..... Page 195

Circulatory Changes in Patients with Coronary Artery Disease Following Thiamylal-Succinylcholine and Tracheal Intubation ..... Page 232

Table of Contents ..... Page (4)

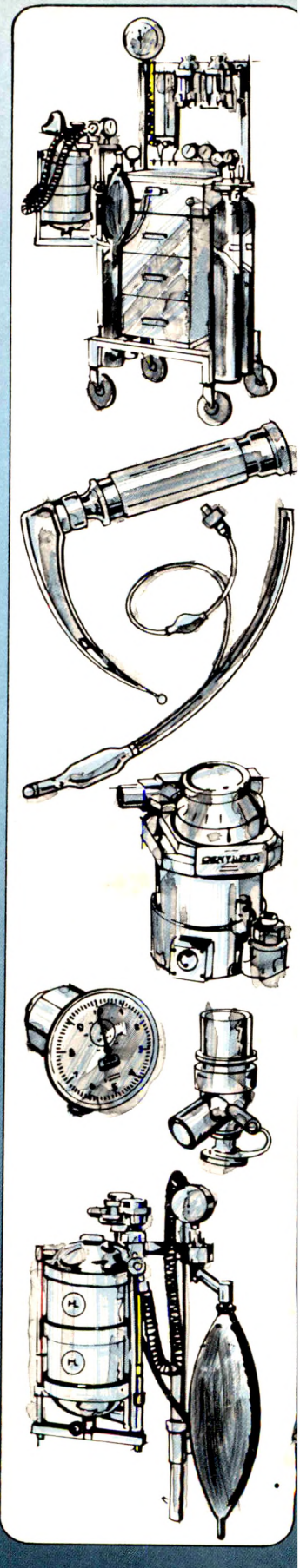
Oldest Publication in the Specialty - Established 1922

Journal of the International Anesthesia Research Society

Volume 55, No. 2 March-April, 1976

51st Congress

Hollywood, Florida - March 6-10, 1977



HARRIS-LAKE, INC.

CLEVELAND, O. / IRVINE, CA. / WILMINGTON, DE.

A new comprehensive catalog is available from Harris-Lake: Anesthesia Equipment and Accessories; Ventilators; Group II Equipment; Wall Rail; Modular Cart and Accessories.

For your copy, please write:

HARRIS-LAKE, INC.
10910 Briggs Road
Cleveland, Ohio 44111

Anesthesia AND Analgesia ...CURRENT RESEARCHES

JOURNAL OF THE INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

3645 Warrensville Center Road • Cleveland, Ohio, U.S.A. 44122 • Telephones: (216) 295-1124, 295-1130

EDITORIAL BOARD

Editor: T. H. Seldon, M.D., Rochester, Minnesota

Associate Editors:
John T. Martin, M.D., Toledo, Ohio
Emerson A. Moffitt, M.D., Halifax, Nova Scotia
Dean H. Morrow, M.D., Houston, Texas
Edwin S. Munson, M.D., Gainesville, Florida
Robert K. Stoelting, M.D., Indianapolis, Indiana

Contributing Editors:
Douglas B. Craig, M.D., Winnipeg, Manitoba
E. Paul Didier, M.D., Rochester, Minnesota
Ronald W. Dunbar, M.D., Atlanta, Georgia
Leonard C. Jenkins, M.D., Vancouver, British Columbia
David E. Longnecker, M.D., Charlottesville, Virginia
John J. Savarese, M.D., Boston, Massachusetts
N. Ty Smith, M.D., San Diego, California

ANESTHESIA AND ANALGESIA . . . Current Researches is published bimonthly by the International Anesthesia Research Society, a non-profit scientific and educational corporation of the state of Ohio. Members of the Board of Trustees of the Society are: Kenneth K. Keown, M.D., John T. Martin, M.D., Emerson A. Moffitt, M.D., Dean H. Morrow, M.D., Edwin S. Munson, M.D., B. B. Sankey, M.D., T. H. Seldon, M.D., Robert K. Stoelting, M.D. Emeritus Trustees are: Paul R. Dumke, M.D., Morris J. Nicholson, M.D.

EDITORIAL CORRESPONDENCE and manuscripts should be addressed to: **T. H. Seldon, M.D., Editor, Kahler East—Suite C, Rochester, Minnesota 55901, U.S.A. Telephone: (507) 288-8655.** (See "A Guide for Authors" for information concerning manuscript preparation.) Original articles accepted for publication, or papers presented at the Society's annual scientific meetings which are subsequently published in this Journal become the property of the International Anesthesia Research Society, publisher. Reproduction in whole or in part is not permitted except by written consent of the publisher and the author.

BUSINESS CORRESPONDENCE, including subscription and membership payments, single issue purchases, change of address notices, requests for membership applications, should be sent to: **B. B. Sankey, M.D., Executive Secretary and Business Manager, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122. Telephones: (216) 295-1124, 295-1130.**

SUBSCRIPTION RATE: $25.00 per year (6 issues), including postage.

MEMBERSHIP DUES: $25.00 per year, includes a subscription to the Journal. **Membership** available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine or other disciplines who are engaged either in active clinical practice of or research in anesthesiology. **Associate Membership** available to individuals certified, licensed or accredited in anesthesia-related professions (CRNA, ARIT, Physician Assistant). **Educational Membership** (two years for $25.00) available to interns, residents, students in nurse anesthesia and related training programs.

SINGLE ISSUES: $4.50 each for years beginning 1970; $3.00 for years 1954-1969; $2.00 for years 1928-1953. (See "Back Issues Available" or write to Cleveland business office for listing.)

REPRINTS: For single copies, write directly to senior author at address listed on title page. Quantity orders (minimum 100) processed through Cleveland business office, prices on request.

MAILING DATES: Journals mailed 25th of January, March, May, July, September and November. Second Class postage paid at Cleveland, Ohio.

CHANGE OF ADDRESS NOTICES: Send to Cleveland business office by first day of the above months to ensure correct addressing of Journals. Replacement copies of missing Journals will be furnished without charge only if original copy is returned by post office as undeliverable.

ADVERTISING: Rate sheets, including advertising clearance procedure, available from national advertising representative: Charles B. Slack, Inc., 6900 Grove Road, Thorofare, New Jersey 08086—Telephone: (609) 848-1000. Orders, contracts, reproduction materials, set copy and classified ad copy should be sent only to Cleveland office.

©1976, International Anesthesia Research Society.

Contents

Volume 55 March-April, 1976 Number 2

SCIENTIFIC ARTICLES

A TECHNIC OF GENERAL ANESTHESIA FOR BLEPHAROPLASTY AND RHYTIDECTOMY—Katz, Machida, Wootton and Amonic 165

CARDIOVASCULAR DYNAMICS AFTER LARGE DOSES OF FENTANYL AND FENTANYL PLUS N_2O IN THE DOG—Liu, Bidwai, Stanley and Isern-Amaral 168

ANESTHETIC CONSIDERATIONS IN DIFFUSE BLEEDING DIATHESIS OF UNCERTAIN ORIGIN—Dalal, Bennett, Grundy, Younes and Orfei 173

"PENTAZEPAM" (PENTAZOCINE + DIAZEPAM) SUPPLEMENTING LOCAL ANALGESIA FOR LAPAROSCOPIC STERILIZATION—Aldrete, Tan, Carrow and Watts 177

SURVIVAL FOLLOWING MASSIVE PULMONARY HEMORRHAGE COMPLICATING PULMONARY EMBOLECTOMY: A CASE REPORT—Wollman and Kushins 182

BACTERIOLOGIC ASPECTS OF EPIDURAL ANALGESIA—James, George, Naiem and White 187

RESECTION OF STENOTIC TRACHEA: A CASE PRESENTATION—Boyan and Privitera ... 191

FACTORS INFLUENCING CHOICE BETWEEN TRACHEOSTOMY AND PROLONGED TRANSLARYNGEAL INTUBATION IN ACUTE RESPIRATORY FAILURE: A PROSPECTIVE STUDY—El-Naggar, Sadagopan, Levine, Kantor and Collins 195

CARDIOVASCULAR EFFECTS OF CANNABINOL DURING ORAL SURGERY — Gregg, Campbell, Levin and Elliott 203

MANAGEMENT OF A PARTURIENT WITH CARDIAC VALVE PROSTHESIS—Saka and Marx 214

A POTENTIAL IGNITION SOURCE IN THE OPERATING ROOM—Anderson 217

THE INTERACTION BETWEEN d-TUBOCURARINE, PANCURONIUM, POLYMYXIN B, AND NEOSTIGMINE ON NEUROMUSCULAR FUNCTION—Van Nyhuis, Miller and Fogdall 224

INCIDENCE OF PROLONGED PAIN RELIEF FOLLOWING ACUPUNCTURE—Lee, Modell, Andersen and Saga 229

CIRCULATORY CHANGES IN PATIENTS WITH CORONARY ARTERY DISEASE FOLLOWING THIAMYLAL-SUCCINYLCHOLINE AND TRACHEAL INTUBATION—Stoelting and Peterson 232

FAILURE TO INDUCE HEPATIC PATHOLOGY IN ANIMALS SENSITIZED TO A HALOTHANE METABOLITE AND SUBSEQUENTLY CHALLENGED WITH HALOTHANE—Reves and McCracken 235

ATYPICAL PSEUDOCHOLINESTERASE: A CLINICAL REPORT—Lear, Jadwat, Bough and Fernandez 243

ANESTHETIC CONSIDERATIONS IN PATIENTS WITH GAS GANGRENE—Laflin, Tobey and Reves 247

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
WE STRIVE ALWAYS FOR WORLD CONQUEST OF PAIN
1922

Anesthesia AND Analgesia . . . Current Researches

SCIENTIFIC ARTICLES—March-April, 1976 (Continued)

THEORETIC SIGNIFICANCE OF pH DEPENDENCE OF NARCOTICS AND NARCOTIC ANTAGONISTS IN CLINICAL ANESTHESIA—Benson, Kaufman and Koski 253

MANAGEMENT OF INTRACTABLE PAIN IN ADIPOSIS DOLOROSA WITH INTRAVENOUS ADMINISTRATION OF LIDOCAINE—Iwane, Maruyama, Matsuki, Ito and Shimoji ... 257

THOUGHTS ABOUT MEDICAL WRITING. XXXIV. THE PUBLICATION PROCESS—Roland 261

A COMPARATIVE STUDY OF ENFLURANE AND HALOTHANE USING SYSTOLIC TIME INTERVALS—Kaplan, Miller and Bailey 263

EFFECT OF $Paco_2$ ON O_2 CONSUMPTION DURING CARDIOPULMONARY BYPASS IN MAN—Patterson 269

THE EFFECTS OF DOXAPRAM ON CEREBRAL BLOOD FLOW AND PERIPHERAL HEMODYNAMICS IN THE ANESTHETIZED AND UNANESTHETIZED GOAT—Miletich, Ivankovich, Albrecht, Bonnet and Reimann 279

ETOMIDATE: AN ULTRASHORT-ACTING NONBARBITURATE AGENT FOR ANESTHESIA INDUCTION—Gooding and Corssen 286

THE INFLUENCE OF SUCTION CATHETER TIP DESIGN ON TRACHEOBRONCHIAL TRAUMA AND FLUID ASPIRATION EFFICIENCY—Link, Spaeth, Wahle, Penny and Glover 290

CASE HISTORY NUMBER 89: A LIFE-THREATENING COMPLICATION OF CRICOTHYROID MEMBRANE PUNCTURE—Poon 298

BRIEF REPORTS

AN UNUSUAL PROBLEM IN NASOTRACHEAL EXTUBATION—Sklar, Alfonso and King 302

A SIMPLE METHOD OF INSERTING A NASOGASTRIC TUBE FOR ANESTHESIA—Baraka 303

ACUTE CARDIOVASCULAR COLLAPSE AFTER INTRAVENOUS PHYTONADIONE—Barash, Kitahata and Mandel 304

FEATURES

People and Places ..... (15)
We Salute—Douglas W. Eastwood, M.D. 185
The Physician and The Law 202
Editor's Choice 219
Correspondence 260
Questions and Answers 274
Scientific Articles, Next Issue ..... (35)
A Guide for Authors ..... (36)
Back Issues Available ..... (38)
Classified Advertising ..... (53)
Something New ..... (56)
Index of Advertisers ..... (60)

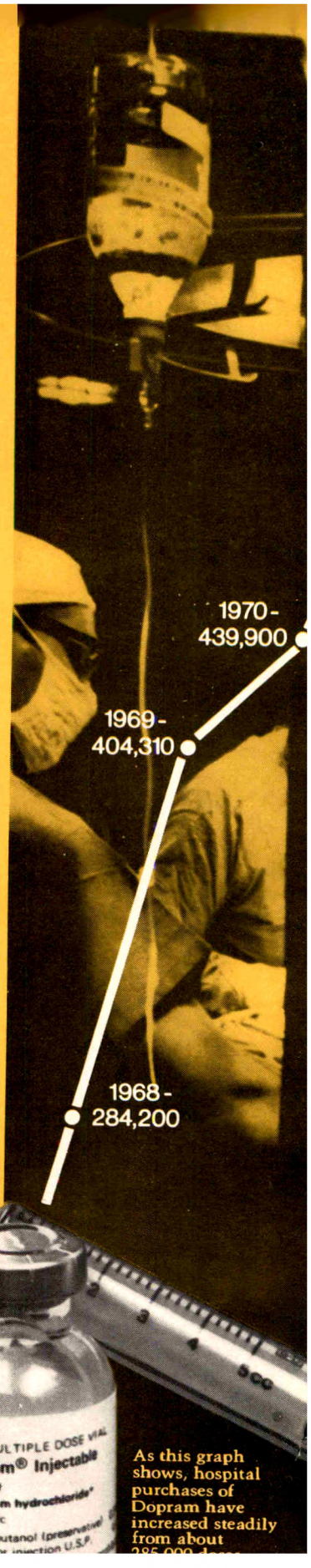
In all types of hospitals across the United States, its usage grows–

Dopram®
Injectable
(doxapram HCl)

Seven years ago, A. H. Robins introduced Dopram, a unique respiratory stimulant developed in the company's research laboratories. What made this drug so useful to the anesthesiologist was its ability to rapidly restore the respiratory drive in patients with drug-induced post anesthetic depression.

Usage of Dopram has been steadily increasing each year, until today it has become a very important drug in the armamentarium of more than 1,500 hospitals of all types in all 50 states, the District of Columbia, and a number of foreign countries. These hospitals purchased more than 600,000 doses in 1972 alone.

Dopram–an important drug in anesthesiology. Try it for sighs!



As this graph shows, hospital purchases of Dopram have increased steadily from about

Indications

1. To stimulate respiration in patients with drug induced post-anesthetic respiratory depression or apnea other than that due to muscle relaxant drugs.
2. To pharmacologically stimulate deep breathing in the so-called "stir-up" regimen in the post-operative patient. Simultaneous administration of oxygen is desirable.
3. To hasten arousal and return of protective pharyngeal and laryngeal reflexes.
4. To aid in the differential diagnosis of post-anesthetic respiratory depression. Failure to adequately stimulate respiration suggests residual muscle relaxant effect.
5. To stimulate respiration, hasten arousal and to encourage the return of laryngopharyngeal reflexes in patients with mild to moderate respiratory and CNS depression due to drug overdosage.

Contraindications—Epilepsy and other convulsive states: incompetence of the ventilatory mechanism due to muscle paresis, flail chest, pneumothorax, airway obstruction, and extreme dyspnea; severe hypertension and cerebrovascular accidents; hypersensitivity.

Doxapram is not recommended for patients 12 years of age or under because studies to evaluate its safety and efficacy have not been performed.

Warnings—Doxapram is an analeptic agent; it is neither an antagonist to muscle relaxant drugs nor a specific narcotic antagonist. Since doxapram has an acid pH, it should not be mixed with alkaline solutions such as thiopental sodium.

Since narcosis may recur after stimulation with doxapram, care should be taken to maintain close observation until the patient has been fully alert for 1/2 to 1 hour. (Duration of drug 5-12 minutes.)

Doxapram is an adjunct to well-accepted supportive measures and resuscitative techniques. It may not stimulate adequate spontaneous breathing or provide sufficient arousal in patients who are severely depressed with CNS depressant drugs.

When doxapram is administered to postoperative patients or to patients in a state of narcosis with chronic pulmonary insufficiency, oxygen should be administered concomitantly. Failure to do so may result in further oxygen debt and more severe dyspnea due to the increased work of breathing.

Doxapram should be administered with great care and only under close supervision to patients with cerebral edema, bronchial asthma, severe tachycardia, cardiac arrhythmia, cardiac disease, hyperthyroidism and pheochromocytoma.

Usage in pregnancy

No adequate clinical studies have been performed to determine the safe use of doxapram in pregnancy. Until further clinical experience has been obtained, the physician must weigh the need against possible risks in using the drug in pregnant patients or in women of child-bearing potential.

Precautions—Recommended dosages of doxapram should be employed and maximum total dosages should not be exceeded. In patients with advanced pulmonary disease with hypoxemia, marked respiratory stimulation increases the work of breathing and may, thus, increase oxygen consumption and carbon dioxide production.

With excessive dosage, hyperventilation induced by doxapram may lead to respiratory alkalosis and hypocapnia with tetany and, theoretically, apnea.

An adequate airway is essential. In order to avoid side effects, it is advisable to use the minimum effective dosage. Monitoring of the blood pressure and deep tendon reflexes is recommended to prevent overdosage.

It is desirable that blood gases (P_{O_2} P_{CO_2} O_2 saturation) be monitored to assess the effectiveness of respiratory stimulation.

Intravenous barbiturates, oxygen and resuscitative equipment should be readily available to manage overdosage manifested by excessive central nervous system stimulation. Slow administration of the drug and careful observation of the patient during administration and for some time possibility of post-stimulation respiratory depression must be kept in mind. In patients who have been lightly curarized, doxapram may temporarily mask the residual effects of muscle relaxant drugs.

Doxapram should be administered cautiously to patients receiving sympathomimetic or monoamine oxidase inhibiting drugs, since a synergistic pressor effect may occur. It should likewise be used with care in post-operative patients with marked dyspnea due to obstructive pulmonary emphysema, acute or chronic asthma, profound metabolic disorders, severe to moderately severe hypertension, increased cerebrospinal fluid pressure, head injury and acute agitation.

Since doxapram may stimulate basal gastric secretion, it should be used with care in patients with peptic ulcer disease and in patients undergoing gastric surgery.

Vascular extravasation or use of a single injection site over an extended period should be avoided since either may lead to thrombophlebitis.

Hypocapnia accompanying forced ventilation is a potent stimulus to cerebral vasoconstriction; it may be postulated that some element of risk may exist from reduced cerebral blood flow following prolonged and intensive hyperventilation.

Since an increase in epinephrine release has been noted with doxapram, it is recommended that initiation of therapy with this respiratory stimulant be delayed for at least 10 minutes following the discontinuance of anesthetics known to sensitize the myocardium to catecholamines, such as halothane and cyclopropane.

As with other intravenous preparations, all precautions should be taken during administration of doxapram to insure that injection is made directly into a suitable vein; extravasation, and inadvertent intra-arterial injection should be avoided.

Adverse reactions—The following adverse reactions have been reported: *Central and Autonomic Nervous Systems.* Hyperactivity, feeling of warmth, sweating, muscle tremor, clonus, increased deep tendon reflexes, dizziness, muscle spasticity, pyrexia, confusion, paresthesia, pupillary dilatation, pilomotor erection, headache, bilateral babinski, fasciculation and carpopedal spasm. A grand mal seizure occurred 95 minutes after drug administration in a known epileptic patient who was on anticonvulsant medication.

Respiratory. Cough, dyspnea, laryngospasm, bronchospasm and hiccough.

Cardiovascular. Hypertension, sinus tachycardia, bradycardia, extrasystoles, lower T-waves, premature ventricular contractions, irregular heart rhythm, tightness in chest. Although a mild to moderate increase in blood pressure is not infrequent, such an increase may occasionally be of concern in hypertensive patients.

Gastrointestinal. Nausea and/or vomiting, salivation, stimulation of lower bowel, sour taste.

Genitourinary. Urinary retention, stimulation of urinary bladder with spontaneous voiding.

Miscellaneous. Pruritus, thrombophlebitis.

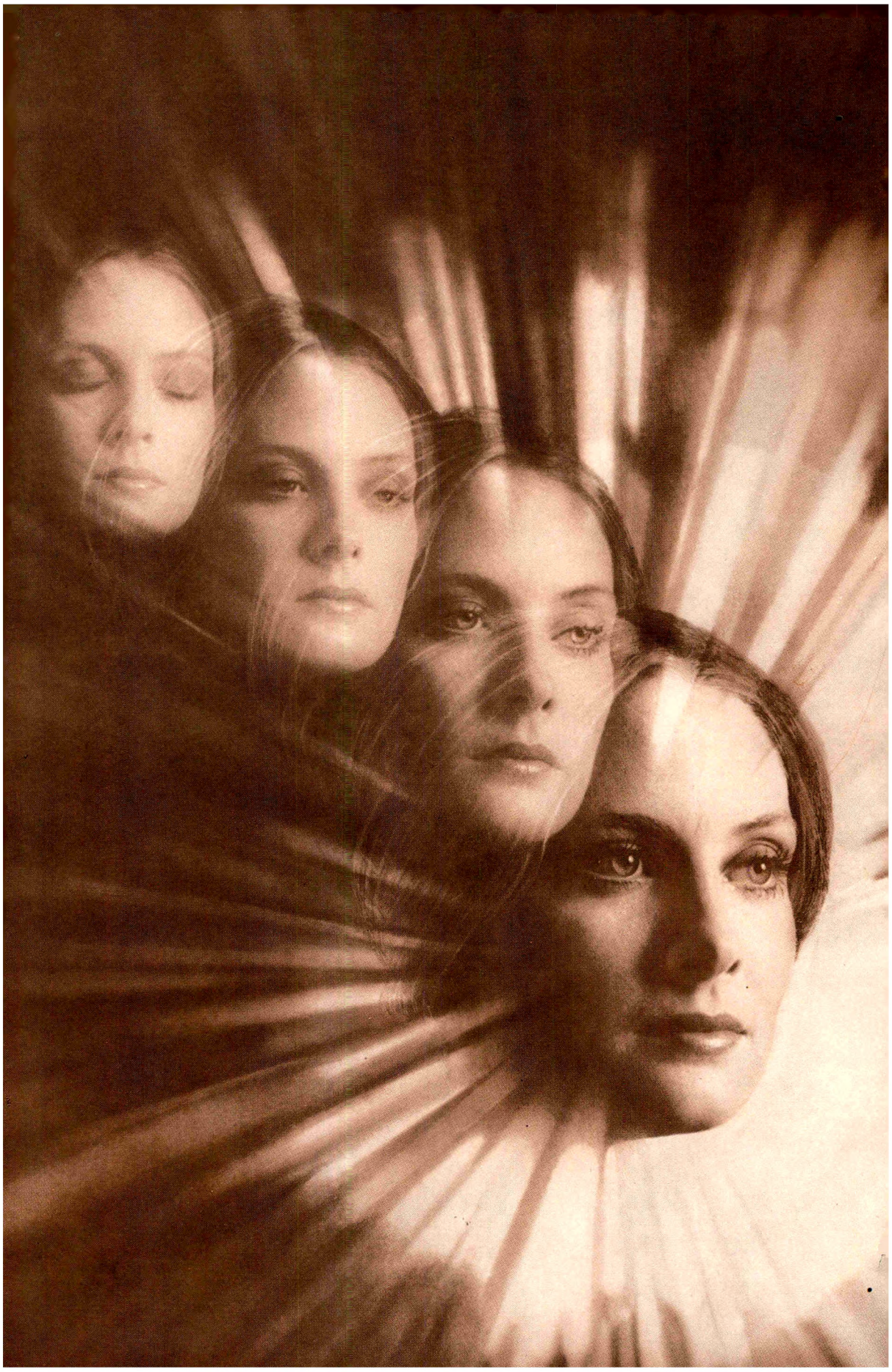
Laboratory Determinations. A decrease in hemoglobin, hematocrit, or red blood cell count has been observed in postoperative patients. In the presence of pre-existing leukopenia, a further decrease in WBC was observed following anesthesia and treatment with doxapram hydrochloride. Elevation of BUN and albuminuria have been observed.

In some of the cases cited above, the patients had received multiple drugs concomitantly, thus preventing an absolute judgment as to the role of doxapram in these reactions.

Dosage—For complete information concerning dosage and administration see package insert.

Supply—Dopram (doxapram hydrochloride) is available in 20 cc rubber stoppered vials containing 20 mg/cc, with chlorobutanol 0.5% as the preservative.

A. H. Robins Company
Richmond, Virginia 23220



A "quick recovery" anesthetic for short surgical procedures

Ethrane® (enflurane) fulfills your anesthetic requirements for short surgical procedures.

Fast Induction, Rapid Recovery. The low blood/gas partition coefficient of ETHRANE (1.91 at 37°C) assures rapid patient induction with minimal excitation. Its mild, pleasant odor is highly acceptable and ETHRANE does not stimulate increased salivation or affect bronchomotor tone.[1] Pharyngeal and laryngeal reflexes can be quickly and easily obtunded. Following anesthesia, because of its low blood solubility, ETHRANE is promptly eliminated at the lungs, permitting rapid emergence and recovery.[2]

Stable Cardiac Rhythm. Cardiac rhythm usually remains normal during ETHRANE anesthesia and is not altered even with elevations in arterial carbon dioxide.[3] Although nodal or atrial arrhythmias occasionally appear, ventricular extrasystoles are rare. Heart rate is sustained at preanesthetic levels. Bradycardia or tachycardia do not normally occur. Blood pressure tends to be reduced with induction, but this effect is reversed with surgical stimulation.[4]

Excellent Muscle Relaxation. At clinical concentrations, ETHRANE usually provides muscle relaxation sufficient for lower abdominal procedures. In addition, relaxation is often adequate for procedures of the upper abdomen. If greater relaxation is required, its potentiation of nondepolarizing relaxants reduces the dosage of such adjunctive neuromuscular blocking agents.[4]

Few Anesthetic Aftereffects. Following cessation of anesthesia with ETHRANE, recovery is rapid, uneventful, and complete. Postoperative return of adequate pulmonary ventilation is rapid.[1] Nausea, vomiting, and delirium are rare. Usually there is an early return of lucidity, desire for fluids, and generally a feeling of well-being.[1,5]

WARNING: Motor activity exemplified by movement of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia. For additional warnings, contraindications, and precautions, see following page.

Films Available for Medical Education. As a service to the anesthesia profession, Ohio Medical Products has available, without charge, motion pictures for use in continuing medical education. Topics include such areas as "Management of Ambulatory Surgical Procedures" and "The Use of ETHRANE." To arrange for a personal or group showing, contact your OHIO Anesthetic Representative, or write to our Communications Department in Madison, Wisconsin.

Ethrane®
(enflurane)

Versatile in Concept–Versatile in Performance

Ohio Medical Products
3030 AIRCO DRIVE
MADISON, WISCONSIN 53701

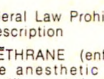
AIRCO®

See following page for full disclosure

Ethrane® (enflurane) Versatile in concept... Versatile in performance.

CAUTION: Federal Law Prohibits Dispensing without Prescription

Description: ETHRANE (enflurane) is a nonflammable anesthetic agent. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



Some physical constants of the compound are:

Molecular weight	184.5
Boiling point 760 mm Hg.	56.5°C
Refractive index n_D^{20}	1.3026-1.3030
Specific gravity 25°/25°C	1.517
Vapor pressure in mm Hg.**	20°C 174.5 25°C 217.7 36°C 345.2

**Equation for calculation of enflurane vapor pressures:

$$\log_{10} P = A + \frac{B}{T}$$

A = 7.967
B = −1678.4
T = °C + 273.16 (Kelvin)

Partition coefficients @ 37°C	
Water-gas	0.82
Blood-gas	1.91
Oil-gas	98.5
Partition coefficients @ 25°C—rubber and plastic	
Conductive rubber	74.0
Butyl rubber	90.0
Polyvinylchloride	120.0
Polyethylene	≈2.0
Polyurethane	≈1.5
Polyolefin	≈1.2
Butyl acetate	≈3.0
Solubility of enflurane in H_2O at 22°C	0.275%
Solubility of H_2O in enflurane	0.13%
Purity by gas chromatography	>99.9%
Flammability in air	None
Flammability in oxygen (Entire concentration range to saturation at 71 and 113°F and 743 mm Hg. pressure.)	None
M.A.C. (Minimum alveolar concentration)	
Man with pure oxygen	1.68
Man with 70% nitrous oxide	0.56 (est.)

ETHRANE is a clear, colorless, stable liquid without added chemical stabilizers. ETHRANE has a mild, sweet odor. Storage of samples in indirect sunlight in clear, colorless glass for a five year period, as well as direct exposure for 30 hours to a 2 amp, 115 V., 60 cycle long wave U.V. light, produced no changes in composition detectable by gas chromatography. ETHRANE in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed none of the alkali, indicative of strong base stability. ETHRANE does not decompose in contact with soda lime. ETHRANE does not attack aluminum, tin, brass, iron or copper.

Actions: ETHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ETHRANE are rapid. ETHRANE does not appear to stimulate excess salivation or tracheobronchial secretions, or affect bronchomotor tone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ETHRANE. ETHRANE reduces ventilation as depth of anesthesia increases. ETHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm. ETHRANE sensitizes the myocardial conduction system to epinephrine in dog and can produce serious arrhythmias. Comparable information in man is not available.

Muscle relaxation is adequate for intra-abdominal operation at normal levels of anesthesia. Should greater relaxation be necessary, minimal doses of muscle relaxants may be used. All commonly used muscle relaxants are compatible with ETHRANE. **The nondepolarizing muscle relaxants are markedly potentiated.** Neostigmine does not reverse the direct effect of ETHRANE.

Biotransformation of ETHRANE (enflurane) in man results in low levels of serum fluoride ions averaging 15 mM/L. These levels are well below the 50 mM/L seen to produce renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation.

Indications: ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

Contraindications: Seizure disorders (see WARNINGS).

Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.

Warnings: Increasing depth of anesthesia with ETHRANE (enflurane) produces a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by hyperventilation producing low arterial carbon dioxide tension. The pattern serves as a warning that depth of anesthesia is excessive. Cerebral blood flow and metabolism studies in normal volunteers during seizure patterns show no evidence of cerebral hypoxia, and recovery appears to be uncomplicated.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. With deep levels of anesthesia, more marked hypotension and respiratory depression are encountered.

The action of nondepolarizing relaxants is augmented by ETHRANE. Less than the usual amounts of these drugs should be used. The time for recovery from the myoneural effect of these relaxants is greater in the presence of ETHRANE than for other commonly used anesthetics.

The safety of the use of epinephrine topically and subcutaneously has not been established in man.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

Precautions: Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ETHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ETHRANE.

Adverse reactions: 1. Motor activity exemplified by movement of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia. 2. Hypotension and respiratory depression have been reported. 3. Arrhythmias, shivering, nausea, and vomiting have been reported. 4. Elevation of the white blood count has been observed. It has not been determined whether this is related to ETHRANE or to surgical stress.

Dosage and administration: The concentration of ETHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ETHRANE;
b) vaporizers from which delivered flows can easily and readily be calculated.

Maintenance concentration should not exceed 3%. Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ETHRANE and the heart rate remains constant. The use of anticholinergic drugs is a matter of choice.

Induction: Induction may be achieved using ETHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ETHRANE mixture. In general, inspired concentrations of 3.5-4.5% ETHRANE produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be attained with 1.5-3.0% concentration. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm range is preferred to hyper- or hypoventilation in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ETHRANE concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration; establish that the airway is clear and initiate assisted or controlled ventilation with pure oxygen as circumstances dictate.

Administration equipment: ETHRANE (enflurane) may be administered from a flow-through type vaporizer manufactured and specifically calibrated for ETHRANE. Vaporizers which deliver saturated vapor at reasonable flows but are not specifically calibrated for ETHRANE may be used.

ETHRANE contains no stabilizer. Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Packaging: ETHRANE (enflurane) is packaged in 125 and 250 ml. amber bottles. No additives or stabilizers are present.

References:

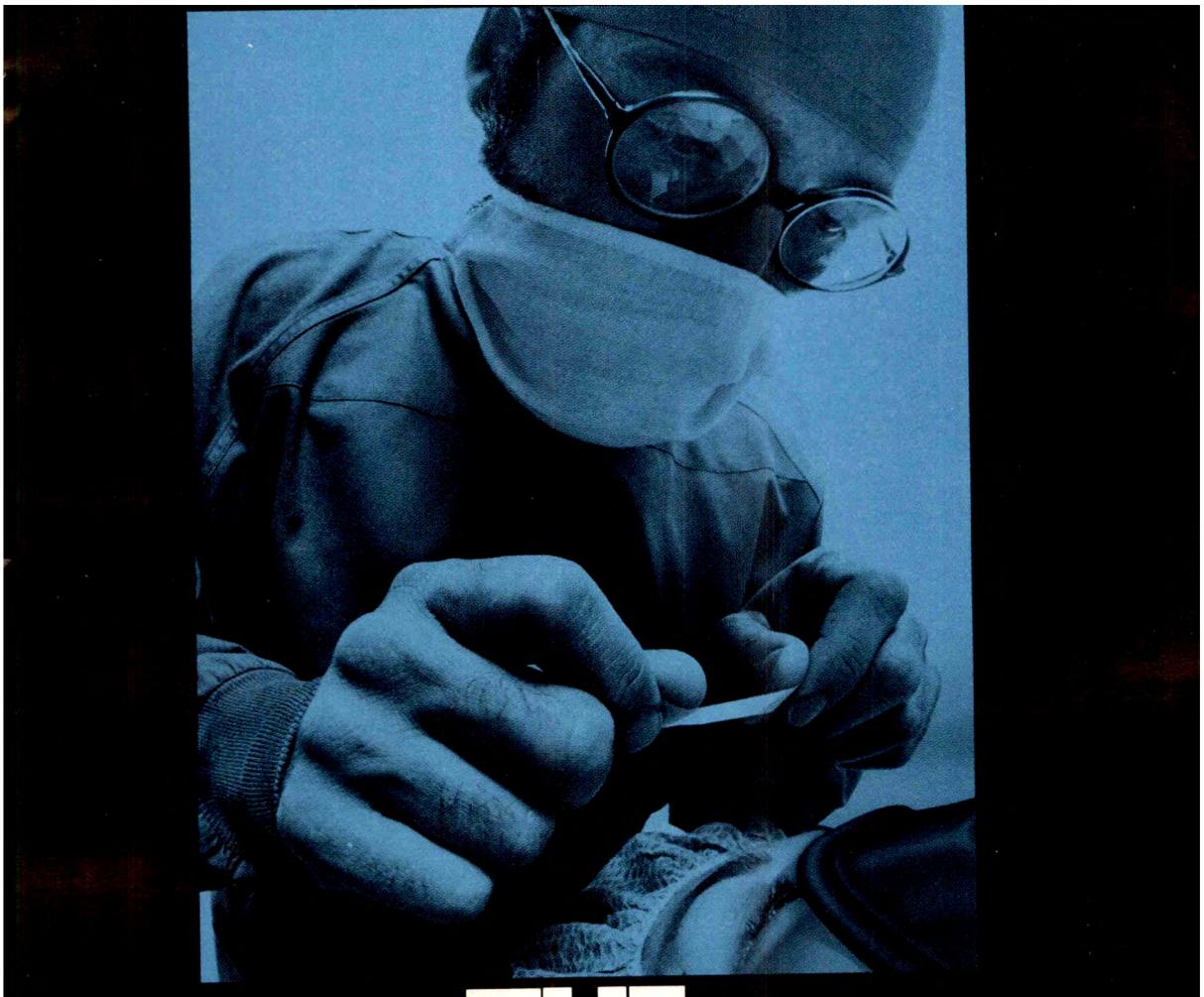
1. Dobkin, A. B., et al: Ethrane (Compound 347) Anesthesia: A Clinical and Laboratory Review of 700 Cases. Anesthesia and Analgesia **48**:477-494, May-June, 1969.

2. Torri, G., et al: Uptake and Elimination of Enflurane in Man. A Comparative Study between Enflurane and Halothane. British Journal of Anaesthesia. **44**:789-794, August, 1972.

3. Marshall, B.E., et al: Some Pulmonary and Cardiovascular Effects of Enflurane (Ethrane) Anesthesia with Varying $PaCO_2$ in Man. British Journal of Anaesthesia. **43**:996-1002, November, 1971.

4. Botty, C., et al: Clinical Experiences with Compound 347, A Halogenated Anesthetic Agent. Anesthesia and Analgesia **47**:499-505, September-October, 1968.

5. Lebowitz, M.H., et al: Clinical Investigation of Compound 347 (Ethrane). Anesthesia and Analgesia. **49**:1-10, January-February, 1970.



THE VULNERABLE EYE.

Lacri-Lube® protects the vulnerable eye of the anesthetized patient.

The under-protected eye is threatened during general anesthesia. Tape alone can leave your patient's eye vulnerable to dehydration and corneal erosion. And with medicated ointments, you unnecessarily risk allergic reactions and possible long-term sensitization.

Lacri-Lube meets your need for a safer, more sophisticated method of protecting and lubricating the eye. Either on its own or as an adjunct to taping. It's the first non-medicated, sterile ophthalmic ointment specifically designed to lubricate and protect the eye — and do nothing more.

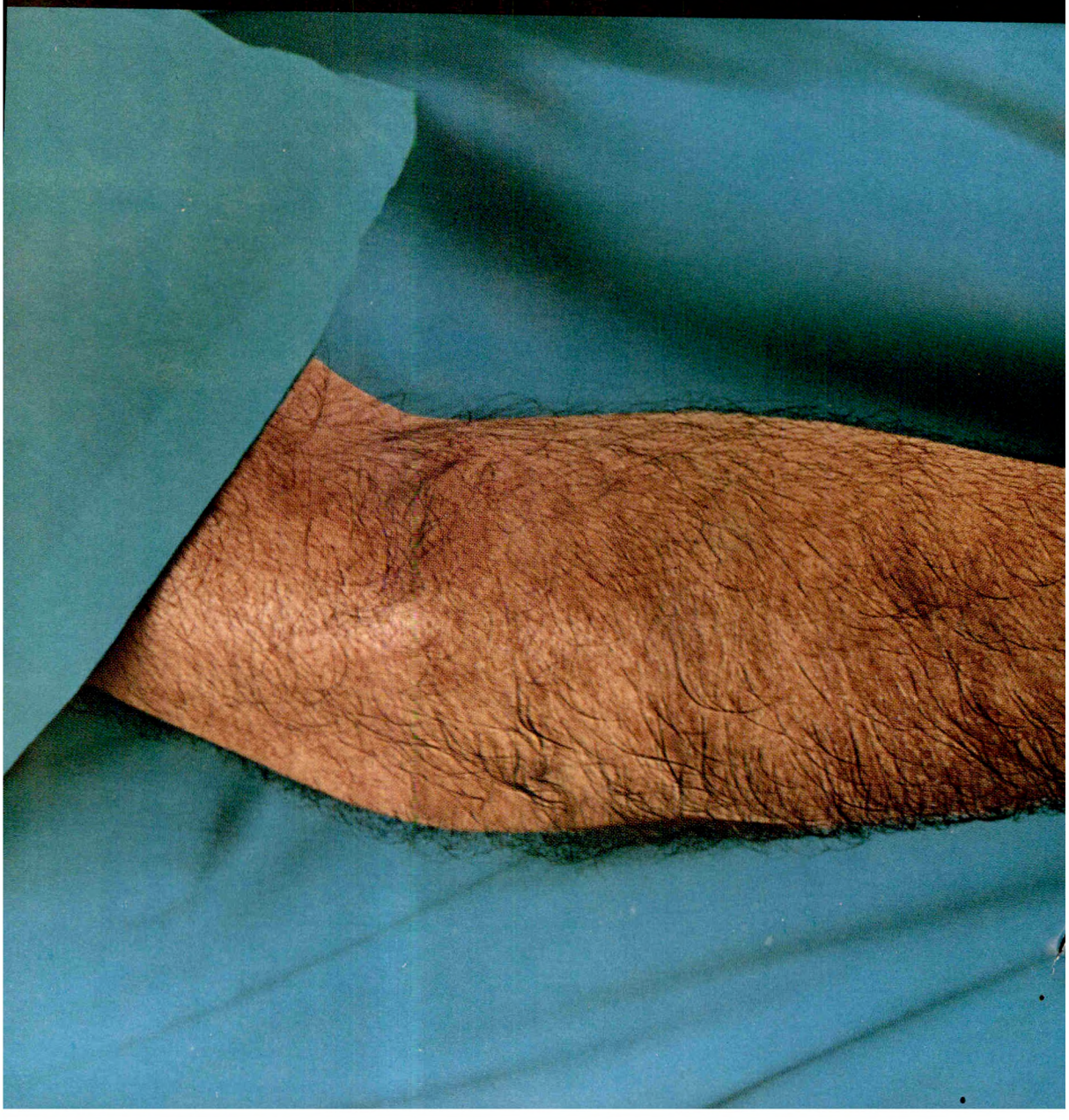
In fact, ophthalmologists have established Lacri-Lube as their lubricant-protectant of choice whenever an eye is jeopardized by exposure or dehydration. And the rapid increase in its surgical use indicates that Lacri-Lube fulfills the same need among anesthesiologists.

Lacri-Lube is the ophthalmic for anesthesia.

When you consider the alternatives, you can't make a better choice.

ALLERGAN
Irvine, CA 92664

Take the Excessive Anxiety out of Anesthesia



Vistaril I.M. (hydroxyzine HCl) helps allay the anxiety that may complicate premedication, induction and recovery room emergence.

It has no significant depressant effects on respiratory or circulatory function and often reduces postoperative emesis.

Vital signs are seldom impaired. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.

And, because it may enhance the effect of injectable analgesics, requirements of narcotic and nonnarcotic analgesics, such as meperidine, morphine sulfate and pentazocine, may be reduced.

Vistaril I.M. is physically compatible with most commonly used analgesics, and can be mixed with them in the same syringe.

Alone, or as an adjunct for use with injectable analgesics, the maximum recommended dosage of Vistaril I.M. is 100 mg. While the analgesic dosage needed will usually be reduced, the actual dosage of Vistaril I.M. should be titrated against the individual patient's clinical response.

Vistaril® I.M.
(hydroxyzine HCl)
100 mg./2 ml., 50 mg./ml. and 25 mg./ml. Vials and Isojects®

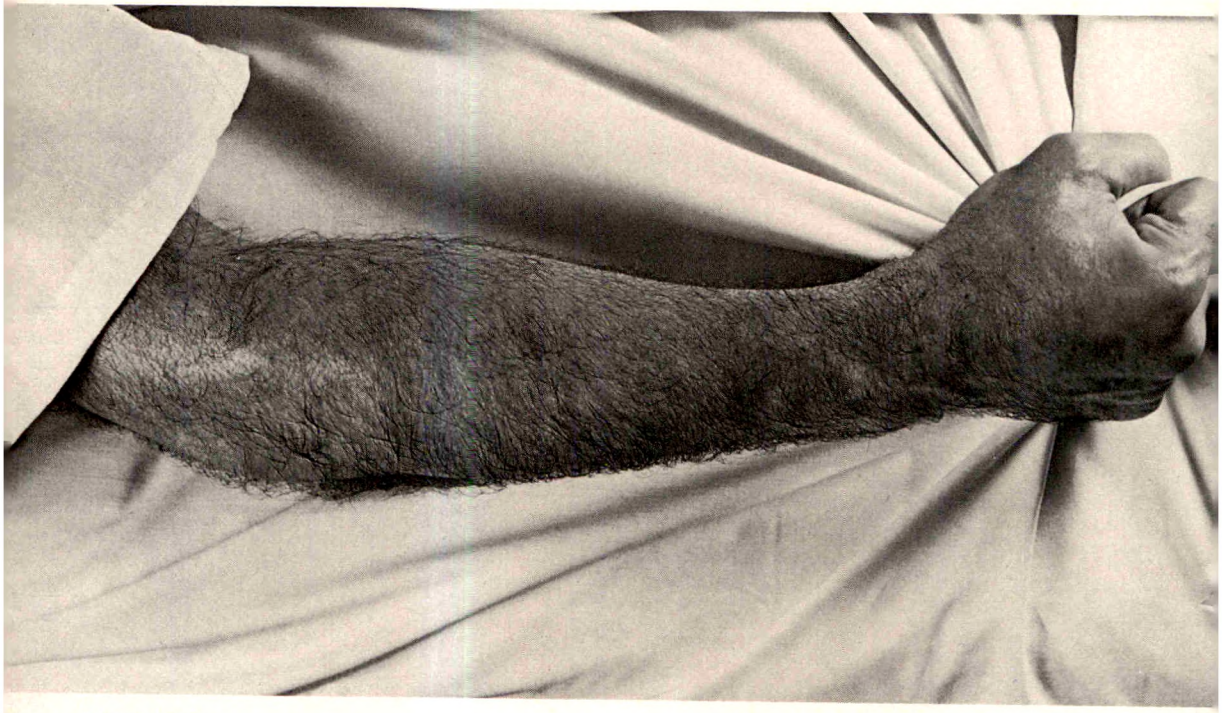
Pfizer
LABORATORIES DIVISION
PFIZER INC.

Please see Brief Summary on following page for contraindications, precautions and adverse reactions.

Vistaril® I.M.
(hydroxyzine HCl)

100 mg./2 ml., 50 mg./ml. and 25 mg./ml.
Vials and Isojects®

Calm Before Anesthesia... In Recovery



Brief Summary
VISTARIL® (hydroxyzine hydrochloride) Intramuscular Solution
For Intramuscular Use Only

Contraindications: Hypersensitivity to hydroxyzine. The solution for intramuscular use *must not* be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate. Until adequate data are available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: *Hydroxyzine may potentiate the action of central nervous system depressants such as narcotics and barbiturates.* In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscle of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in o to minimize the possibility of damage to the sciatic nerve. The deltoic area should be used only if well developed, such as in certain adults older children, and only with caution to avoid radial nerve injury. Injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid intravascular inject

Adverse Reactions: Drowsiness may occur; if so, it is usually transit and may disappear in a few days of continued therapy or upon dosag reduction. Dryness of the mouth may occur with higher doses. Involu tary motor activity, including rare instances of tremor and convulsion has been reported, usually with higher than recommended dosage.

Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg./m 10 ml. vial; 50 mg./ml.—2 ml. and 10 ml. vial; Isoject®, 25 mg./ml. an 50 mg./ml., 1 ml. fill; 100 mg./2 ml., 2 ml. fill.
Military Depot: NSN 6505-00-052-1367 (50 mg./ml., 10 ml. vial)
VA Depot: NSN 6505-00-052-1367B (50 mg./ml., 10 ml. vial)

More detailed professional information available on request.

Pfizer **LABORATORIES DIVISION**
PFIZER INC.

PEOPLE AND PLACES

The Robert D. Dripps Memorial Conference, sponsored by the Robert D. Dripps Library and the Department of Anesthesia, University of Pennsylvania, will be held April 26, 27, and 28, 1976, at the Hilton of Philadelphia on the University of Pennsylvania Campus, Philadelphia, Pennsylvania.

★ ★ ★

The Postgraduate Continuation Course, "Anesthesia and Current Clinical Practice," sponsored by the Lahey Clinic Foundation Department of Education and Department of Anesthesiology, will be held May 7-8, 1976, at the Copley Plaza Hotel, Boston, Massachusetts.

★ ★ ★

District II, New York State Society of Anesthesiologists and The Department of Anesthesiology, Mount Sinai School of Medicine, will have a workshop on "Anesthetic Pollution" May 8, 1976, in the Stern Auditorium of the Annenberg Building, Fifth Avenue and 100th Street, New York.

★ ★ ★

Harvard Medical School, Department of Continuing Education, announces a course in Obstetric Anesthetic Management, May 14 and 15, 1976, at the Colonnade Hotel, Boston, Massachusetts.

★ ★ ★

The Fourth Annual Postgraduate Seminar in Pediatric Anaesthesia, sponsored by the Department of Anaesthesia, University of Cincinnati Medical Center, will be held May 21, 22, and 23, 1976, at the Quality Inn Riverview, Covington, Kentucky.

★ ★ ★

McGill University, Montreal, Quebec, Canada, will present the Annual Review Course in Anaesthesia in the McIntyre Medical Sciences Building, May 24-28, 1976.

★ ★ ★

The University of Tennessee College of Medicine will present their Continuing Education Course, "Intensive Review of the Basic Medical Sciences as Related to the Study and Practice of Anesthesiology," May 24-28, 1976, at the Wassell Randolph Student-Alumni Center, University of Tennessee Center for the Health Sciences, Memphis, Tennessee.

★ ★ ★

The First National Congress of Anaesthesia and Intensive Care, organized by the Romanian Society of Anesthesia and Intensive Care will be held in Bucharest May 26-28, 1976. For more detailed information write to the Secretariate of the First National Congress of Anaesthesia and Intensive Care—Union of Societies of Medical Sciences, Bucharest 8 Progresului Street, Bucharest, Romania.

The University of West Florida and the Pensacola Educational Program will present a seminar on "Anesthesia and Adjunctive Therapy" May 29 and 30, 1976, at the Galatea Inn, Pensacola Beach, Pensacola, Florida.

★ ★ ★

The annual Scientific Meeting of the California Society of Anesthesiologists to include Refresher Courses and General Sessions will be held at the Hotel Sahara, Las Vegas, Nevada, June 3-6, 1976.

★ ★ ★

A Symposium, "Basic Sciences Related to Anesthesiology and Critical Care," sponsored by the Departments of Anesthesiology, Montefiore Hospital and Medical Center and Albert Einstein College of Medicine, will be presented June 7-11, 1976, at the Montefiore Hospital and Medical Center, Bronx, New York.

★ ★ ★

The Tenth Congress of the Israel Society of Anaesthesiologists will be held at the Hilton Hotel, Jerusalem, on June 10-11, 1976. For further information write to **Dr. E. Levy,** Department of Anesthesia, Beilinson Medical Centre, Petah Tiqva, Israel.

★ ★ ★

The Illinois Society of Anesthesiologists will present the Thirteenth Midwest Anesthesiology Conference, "Anesthetic Challenges in Patients With Medical Problems," June 10, 11, 12, 1976, at the Sheraton-Chicago Hotel, Chicago, Illinois.

★ ★ ★

The VIIth Congress of the Polish Society of Anesthesiologists will be held in Warsaw, Poland in the second half of June 1976.

For further information write to the Secretariat, Lindleya 4, 02-005 Warszawa, Poland.

★ ★ ★

The Canadian Anaesthetists' Society 27th Annual Meeting will be held in Montreal, Quebec, Canada, June 20-24, 1976.

For further information contact: The Secretary, Canadian Anaesthetists' Society, 178 St. George Street, Toronto, Ontario, Canada M5R 2M7.

★ ★ ★

The 28th Annual Workshops and Scientific Program of the Society for Clinical and Experimental Hypnosis, June 26-30, 1976, and the 7th International Congress of Hypnosis and Psychosomatic Medicine, July 1-3, 1976, are sponsored by the University of Pennsylvania (Philadelphia, PA, USA). For information regarding registration and acommodations, write to **Martin T. Orne, MD, PhD,** The Institute of Pennsylvania Hospital, 111 North 49th Street, Philadelphia, PA 19139.

★ ★ ★

The Department of Anesthesiology, Baylor College of Medicine, will present the first in an annual series of postgraduate programs on November 18 and 19, 1976, in the Shamrock Hilton Hotel, Houston, Texas.

The formal title of the program is: "BAY-CAP I, The Patient With Ischemic Heart Disease."

A mainstay of modern anesthesia

- As an adjunct to general anesthesia
- As a supplement to regional anesthesia
- Used without a general anesthetic in certain diagnostic procedures

INNOVAR® injection is available for use only upon direction of a physician.

Special educational material available

A Programmed Instruction Manual on the chemistry, pharmacology and clinical applications of INNOVAR injection and its components is available from McNeil Laboratories. For further information, please write: Product Director, INNOVAR injection, McNeil Laboratories, Inc., Fort Washington, Pa. 19034.

© McN 1975

For prescribing information including Contraindications, Warnings, Precautions and Adverse Reactions, please turn page.

Innovar® injection

The two components of INNOVAR® injection, fentanyl and droperidol, have different pharmacologic actions. Before administering INNOVAR injection, the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action.

DESCRIPTION

Each cc. contains (in a 1:50 ratio):

Fentanyl ..... 0.05 mg.
as the citrate

Warning: May be habit forming

Droperidol ..... 2.5 mg.
Lactic acid for adjustment of pH to 3.5± 0.3

FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY

Protect from Light

ACTIONS INNOVAR injection is a combination drug containing a narcotic analgesic, fentanyl, and a neuroleptic (major tranquilizer), droperidol. The combined effect, sometimes referred to as neuroleptanalgesia, is characterized by general quiescence, reduced motor activity, and profound analgesia; complete loss of consciousness usually does not occur from use of INNOVAR injection alone. The incidence of early postoperative pain and emesis may be reduced.

A. Fentanyl is a narcotic analgesic with actions qualitatively similar to those of morphine and meperidine. Fentanyl in a dose of 0.1 mg. (2.0 cc.) is approximately equivalent in analgesic activity to 10 mg. of morphine or 75 mg. of meperidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. Fentanyl appears to have less emetic activity than other narcotic analgesics. Histamine assays, and skin wheal testing in man, as well as *in vivo* testing in dogs indicate that histamine release rarely occurs with fentanyl.

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. It may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia, and bronchoconstriction.

The onset of action of fentanyl is almost immediate when the drug is given intravenously; however, maximal analgesic and respiratory depressant effect may not be noted for several minutes. The average duration of action of the analgesic effect is 30 to 60 minutes. Following intramuscular administration, the onset of action is from seven to eight minutes, and the duration of action is from one to two hours. Although the duration of the respiratory depressant effect is unknown, as with other narcotic analgesics, it may be considerably longer than the analgesic effect.

B. Droperidol produces marked tranquilization and sedation. It also produces an antiemetic effect as evidenced by the antagonism of apomorphine in dogs. It potentiates other CNS depressants. It also produces mild alpha adrenergic blockade, peripheral vascular dilatation and reduction of the pressor effect of epinephrine. Droperidol can produce hypotension and decreased peripheral vascular resistance. It may decrease pulmonary arterial pressure (particularly if it is abnormally high). It may reduce the incidence of epinephrine-induced arrhythmias but it does not prevent other cardiac arrhythmias. The onset of action is from three to ten minutes following intravenous or intramuscular administration. The full effect, however, may not be apparent for 30 minutes. The duration of the sedative and tranquilizing effects generally is two to four hours. Alteration of consciousness may persist as long as 12 hours. This is in contrast to the much shorter duration of action of fentanyl.

INDICATIONS INNOVAR injection is indicated to produce tranquilization and analgesia for surgical and diagnostic procedures. It may be used as an anesthetic premedication, for the induction of anesthesia, and as an adjunct in the maintenance of general and regional anesthesia. If the supplementation of analgesia is necessary, SUBLIMAZE® (fentanyl) injection alone rather than the combination drug INNOVAR injection should usually be used.

CONTRAINDICATIONS INNOVAR injection should not be used in patients who are hypersensitive to either component.

WARNINGS PATIENTS WHO HAVE RECEIVED *INNOVAR* INJECTION SHOULD BE UNDER APPROPRIATE SURVEILLANCE.

RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INNOVAR injection, the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses, as low as 1/4 to 1/3 those usually recommended.

INNOVAR injection may cause muscle rigidity, particularly involving the muscles of respiration. This effect is due to the fentanyl component and is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs it is managed by the use of assisted or controlled respiration and by a neuromuscular blocking drug, if necessary.

FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD ALSO BE AVAILABLE.

Drug Dependence: *Fentanyl, the narcotic analgesic component, can produce drug dependence of the morphine type and therefore has the potential for being abused.*

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl, in this regard, has not been established, the use of INNOVAR injection or SUBLIMAZE fentanyl in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure: INNOVAR injection should be used with caution in patients who may be particularly susceptible to respiratory depression such as comatose patients who may have a head injury or brain tumor. In addition, these drugs may obscure the clinical course of patients with head injury.

Usage in Children: The safety of INNOVAR injection in children two years of age or younger has not been established.

Usage in Pregnancy: The safe use of INNOVAR injection has not been established with respect to possible adverse effects upon fetal development.

Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS *The initial dose of INNOVAR injection should be appropriately reduced in elderly, debilitated and other poor risk patients. The effect of the initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves, and can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms (see Actions) fentanyl and droperidol also depress respiration and blood pressure. Therefore, when INNOVAR injection is used to supplement these forms of anesthesia, the anesthetist must be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

The droperidol component of INNOVAR injection may decrease pulmonary arterial pressure. This fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient.

Vital signs should be monitored routinely.

INNOVAR injection, and SUBLIMAZE fentanyl, should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised ventilation. In such patients narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia this can be managed by assisted or controlled respiration. Postoperatively respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists (levallorphan, nalorphine, and naloxone); consult individual prescribing information before using.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INNOVAR injection. When patients have received such drugs, the dose of INNOVAR injection required will be less than usual. Likewise, following the administration of INNOVAR injection the dose of other CNS depressant drugs should be reduced.

INNOVAR injection should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in the moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus these other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INNOVAR injection due to the alpha-adrenergic blocking action of droperidol.

The fentanyl component may produce bradycardia, which may be treated with atropine; however, INNOVAR injection should be used with caution in patients with cardiac bradyarrhythmias.

When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

ADVERSE REACTIONS The most common serious adverse reactions reported to occur with INNOVAR injection are respiratory depression, apnea, muscular rigidity, and hypotension; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, twitching, blurred vision, hyperactivity on induction, laryngospasm, transient hypertension, nausea and emesis, diaphoresis, emergence delirium, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).

Postoperative drowsiness is also frequently reported.

OVERDOSAGE ***Manifestations:*** The manifestations of INNOVAR injection overdosage are an extension of its pharmacologic actions.

Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered. A specific narcotic antagonist such as nalorphine, levallorphan or naloxone should be available for use as indicated to manage respiratory depression caused by the narcotic component fentanyl. This does not preclude the use of more immediate countermeasures. Consult the package inserts for the individual narcotic antagonists for details about use.

HOW SUPPLIED INNOVAR® injection is supplied in 2 cc. (**NDC** 0045-0280-20) and 5 cc. (**NDC** 0045-0280-50) ampuls, in packages of 10.

IMPORTANT: Complete dosage information is available in insert which accompanies each package (or on request). The drug is available only upon direction of a physician.

U.S. Patent No. 3,141,823

9/74

McNEIL McNeil Laboratories, Inc.
Fort Washington, Pa. 19034

When you need to know

DINAMAP for **non-invasive,** routine monitoring of arterial pressure.‡

Using: An ordinary pressure cuff with no transducer. Easily attached to any limb.*

Provides: Automatic determination and digital display of mean arterial pressure.

Write or call for your demonstration.

Applied Medical Research
6 Columbia Drive
Tampa, Fla. 33606
(813) 251-8390 Dept. 3

‡Audible pulse monitor optional.
*Including patient preferred ankle.

ANTILIRIUM
(Physostigmine Salicylate)

REVERSES MOST POST-OPERATIVE DELIRIUM AND PROLONGED SOMNOLENCE

Before prescribing, please consult complete product information, a summary of which follows:

ACTION: ANTILIRIUM (physostigmine salicylate) is a salicylic acid derivative of an alkaloid extracted from seeds of Physostigma Venenosum (calabar bean). The action of the parasympathetic nerves is intermediated by the formation of acetylcholine at the peripheral end of these nerves. Physostigmine inhibits the destructive action of cholinesterase and thereby prolongs and exaggerates the effect of the acetylcholine.

Physostigmine contains a tertiary amine and easily crosses the blood brain barrier, while neostigmine contains a quaternary amine and is not capable of crossing the structure. This may explain why neostigmine does not cause reversal of anticholinergic-induced delirium while physostigmine does.

INDICATIONS: TO REVERSE THE TOXIC EFFECTS UPON THE CENTRAL NERVOUS SYSTEM CAUSED BY DRUGS IN CLINICAL OR TOXIC DOSAGES CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING.

SEVERE ANTICHOLINERGIC POISONING MAY PRODUCE:
COMA, MEDULLARY PARALYSIS AND DEATH.

CENTRAL TOXIC EFFECTS MAY INCLUDE: HALLUCINATIONS, DELIRIUM, DISORIENTATION, ANXIETY AND HYPERACTIVITY.

Dramatic reversal within minutes of coma, hallucinations, and other signs can be expected if the diagnosis is correct and the patient has not suffered anoxia or other insult. Therapeutic doses may be necessary at intervals as life-threatening signs recur. Physostigmine is destroyed in the body in 60 to 120 minutes.

CONTRAINDICATIONS: Physostigmine should not be used in the presence of asthma, gangrene, diabetes, cardiovascular disease, mechanical obstruction of the intestines or urogenital tract or any vagotonic state, and in patients receiving choline esters or depolarizing neuromuscular blocking agents.

WARNING: If excessive symptoms of salivation, emesis, urination and defecation occur, the use of ANTILIRIUM should be terminated. If excessive sweating or nausea occur, the dosage should be reduced.

Intravenous administration should be at a slow, controlled rate, no more than 1 mg. per minute (see dosage). Rapid administration can cause bradycardia, hypersalivation leading to respiratory difficulties and possibly convulsions.

An overdosage of ANTILIRIUM can cause a cholinergic crisis.

PRECAUTIONS: Because of the possibility of hypersensitivity in an occasional patient, atropine sulfate injection should always be at hand since it is an antagonist and antidote for physostigmine.

ADMINISTRATION AND DOSAGE: The usual adult dose of ANTILIRIUM is 0.5 to 2.0 mg. intramuscularly or intravenously. Intravenous administration should be at a slow, controlled rate of no more than 1 mg. per minute. It may be necessary to repeat dosages of 1 mg. to 4 mg. at intervals as life threatening signs such as arrhythmias, convulsions and deep coma recur.

IN ALL CASES OF POISONING, THE USUAL SUPPORTIVE MEASURES SHOULD BE UNDERTAKEN.

SUPPLIED: 2 ml. ampules containing:
PHYSOSTIGMINE SALICYLATE 1 mg. per ml.
Packed 12 ampules per box.

NDC 0456-1037-12

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES:

Greene, L. T.: Physostigmine treatment of anticholinergic drug depression in postoperative patients. Anesth & Analg, March-April 1971; 50-2: 222-226.

Rumack, B.: Anticholinergic poisoning: Treatment with physostigmine. Pediatrics, Sept. 1973.

Slovis, T. L., Ott, J. E., Tietelbaum, D. T., and Lipscomb, W.: Physostigmine therapy in acute tricyclic antidepressant poisoning. Clinical Toxicology, 4:451, 1971.

DRUGS AND CHEMICALS CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING:

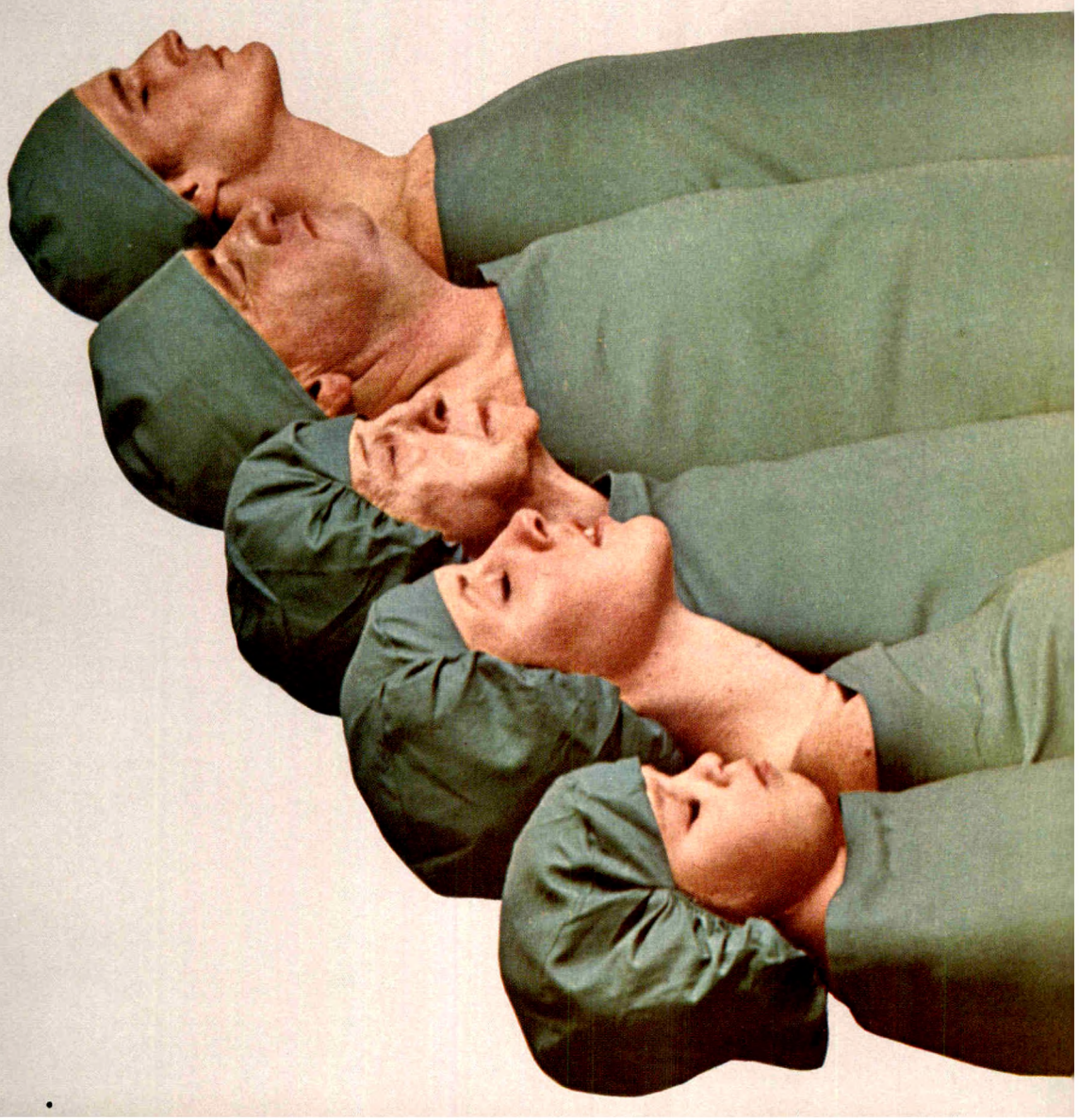
- AMITRIPTYLINE (Elavil, Triavil, Etrafon)
- ANISOTROPINE METHYLBROMIDE
- ATROPINE
- BELLADONNA
- BENACTYZINE
- CHLORPHENIRAMINE
- CYCLOPENTOLATE
- DESIPRAMINE (Norpramin, Pertofrane)
- DICYCLOMINE
- DIPHENHYDRAMINE
- DOXEPIN (Sinequan)
- HOMATROPINE
- HYOSCINE
- HYOSCYAMUS
- IMIPRAMINE (Tofranil, Presamine)
- ISOPROPAMIDE
- MEPENZOLATE
- METHANTHELINE
- METHAPYRILENE
- NORTRIPTYLINE (Aventyl)
- PIPENZOLATE BROMIDE (Piptal)
- PROPANTHELINE
- PROTRIPTYLINE (Vivactil)
- PYRILAMINE
- SCOPOLAMINE
- STRAMONIUM
- PHENOTHIAZINES
- TRICYCLIC ANTIDEPRESSANTS (Aventyl, Elavil, Etrafon, Norpramin, Pertofrane, Presamine, Tofranil, Triavil, Vivactil)
- THIORIDAZINE (Mellaril)

O'NEAL, JONES & FELDMAN, INC.
1304 ASHBY ROAD • ST. LOUIS, MISSOURI 63132 • (314) 997-6650

Clinically proven
nondepolarizing muscle relaxant

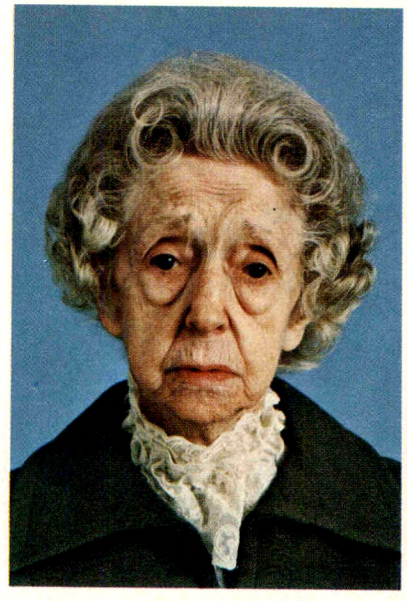
PAVULON®
pancuronium bromide

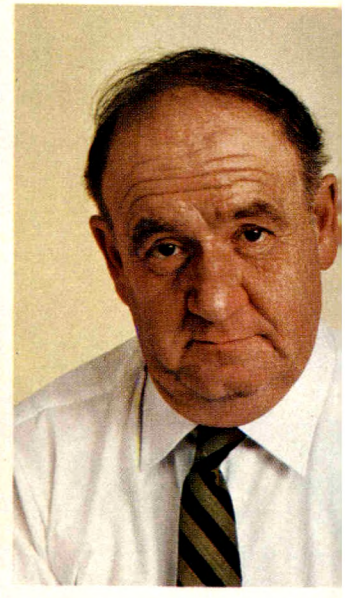
for many patients
for many reasons



An unusually fast-acting nondepolarizing blocking agent [1-5]

PAVULON®
pancuronium bromide





for many patients for many reasons

in pediatric surgery[6-12]

Pavulon® has been used with satisfactory results in pediatric patients undergoing elective surgery[11], abdominal surgery[7] and cardiovascular surgery[8]. Dose response studies indicate that, except for neonates, dosage is the same as for adults. In neonates, a test dose of 0.02 mg/kg is recommended to determine responsiveness.

in geriatric surgery[13]

Pavulon® can be considered a preferred relaxant for major surgical procedures in the aged patient because of the relative absence of significant side effects.

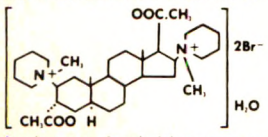
in the high risk patient[2-5, 14-18]

Pavulon® is often preferre for poor risk patients[5,14] especially those with asthn or chronic bronchitis[2,14,16,] cardiovascular disease[4,5,] [18] and patients undergoir abdominal, thoracic or oth major surgery[2,5], includir open heart surgery[15]. Ca tion should be exercise however, in the presence renal disease since a majc portion of the administere drug is excreted unchange in the urine.

PAVULON® (pancuronium bromide)

• THIS DRUG SHOULD ONLY BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: Pavulon (pancuronium bromide) is the aminosteroid 2 beta, 16 beta-dipiperidine-5 alpha-androstane-3 alpha, 17 beta-diol diacetate dimethobromide. It has the following structural formula:



ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon is approximately 5 times as potent as d-tubocurarine chloride.

The onset and duration of action of Pavulon is dose dependent. With the administration of 0.04 mg. per kg. the onset of action, as measured by a peripheral nerve stimulator, is usually within 45 seconds, and its peak effect is usually within 4½ minutes; recovery to 90% of control twitch height usually takes place in less than one hour. Larger doses, more suitable for endotracheal intubation, such as 0.08 mg. per kg. of Pavulon have an onset of action of about 30 seconds, and a peak effect within 3 minutes. Supplemental incremental doses of Pavulon, following the initial dose, slightly increase the magnitude of blockade, and significantly increase the duration of the blockade.

Pavulon has little effect upon the circulatory system. The most frequently reported observation is a slight rise in pulse rate.

Human histamine assays, and clinical observations, as well as in *vivo* guinea pig testing, and in *vitro* mast cell testing, indicate that histamine release rarely, if ever, occurs.

Pavulon is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, kanamycin, and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

Pavulon has no known effect on consciousness, the pain threshold, or cerebration.

INDICATIONS: Pavulon is indicated as an adjunct to anesthesia to induce skeletal muscle relaxation. It may also be employed to facilitate the management of patients undergoing mechanical ventilation.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards. There are insufficient data to support safe use of Pavulon in obstetrics, so such use is not recommended.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: The most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane, and methoxyflurane. No increase in intensity of blockade or duration of action of Pavulon is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. The dosage information which follows has been derived from dose-response studies based on body weight and is intended to serve as a guide only. Since potent inhalational agents or prior administration of succinylcholine enhance the intensity of blockade and duration of Pavulon (see DRUG INTERACTION), these factors should be taken into consideration in selection of initial and incremental dosage.

In adults the initial intravenous dosage range is 0.04 to 0.1 mg. per kg. Later incremental doses starting at 0.01 mg. per kg. may be used. These increments slightly increase the magnitude of the blockade, and significantly increase the duration of blockade, because a significant number of myoneural junctions are still blocked when there is clinical need for more drug.

If Pavulon is used to provide skeletal muscle relaxation for endotracheal intubation, doses of 0.06 to 0.1 mg. per kg. are recommended. Conditions satisfactory for intubation are usually present within 2 to 3 minutes. The ability of the anesthetist to intubate with Pavulon (pancuronium bromide) improves with experience.

Dosage in Children; Dose-response studies in children indicate that, with the exception of neonates, dosage requirements are the same as for adults. Neonates are especially sensitive to nondepolarizing neuromuscular blocking agents, such as Pavulon, during the first month of life. It is recommended that a test dose of 0.02 mg. per kg. be given first in this group to measure responsiveness.

MANAGEMENT OF PROLONGED NEUROMUSCULAR BLOCKADE: Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Pavulon as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade. Under such circumstances the primary treatment is manual or mechanical ventilation and maintenance of a patent airway until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) or neostigmine, in conjunction with atropine, will usually antagonize the skeletal muscle relaxant action of Pavulon. These should be accompanied by or preceded by injection of atropine sulfate to minimize the incidence of cholinergic side effects, notably excessive secretions and bradycardia. Satisfactory reversal can be judged by adequacy of skeletal muscle tone, and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and adjuncts which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade; ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference to the specific package insert of the reversal agents should be made.

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED:

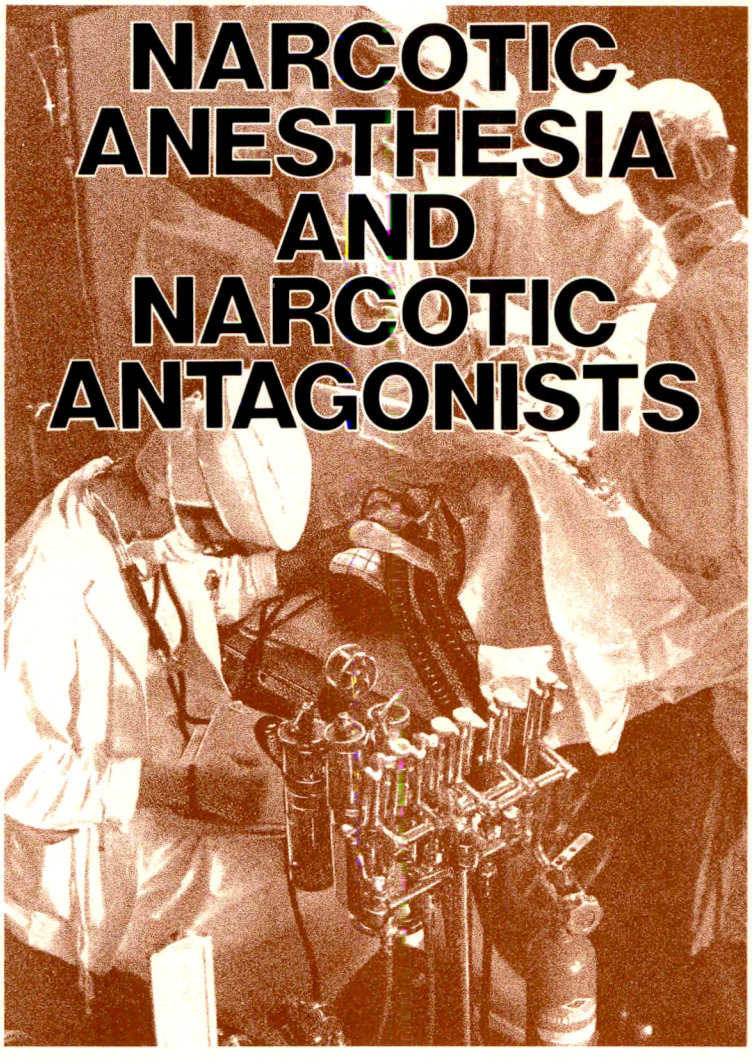
2 ml. ampuls—2 mg./ml.—box of 25
5 ml. ampuls—2 mg./ml.—box of 25
10 ml. multiple dose vials—1 mg./ml.—box of 25

References:

1. Baird, W. L. M. and Reid, A. M.: Brit. J. Anaesth. *39*:775, 1967.
2. McDowell, S.A. and Clarke, R.S.J.: Anaesthesia *24*:581, 1969.
3. Katz, R. L.: Anesthesiology *34*:550, 1971.
4. McIntyre, J. W. R. and Gain, E. A.: Anesth. and Analg. *50*:813, 1971.
5. Dobkin, A.B., *et al.*: Canad. Anaesth. Soc. J.: *18*:512, 1971.
6. Nightingale, D. A. and Bush, G. H.: Brit. J. Anaesth. *45*:63, 1973.
7. Goudsouzian, N. C., Ryan, J. F., and Savarese, J. J.: Anesth. *41*:95, 1974.
8. Bennett, E. J., Dalal, F. Y., and Fisher, M.: M. E. J. Anaesth. 3:413, 1972.
9. Yamamoto, T., Baba, H., and Shiratsuchi, T.: Anesth. and Analg. *51*:919, 1972.
10. Bennett, E. J., Bowyer, D. E., Giesecke, Jr., A. H., and Stephen, C. R.: Anesth. and Analg. *52*:12, 1973.
11. Lippmann, M. and Rogoff, R. C.: Anesth. and Analg. *53*:684, 1974.
12. Bennett, E. J., Daughety, M. J., Bowyer, D. E., and Stephen, C. R.: Anesth. and Analg. *50*:798, 1971.
13. Lorhan, P. H. and Lippmann, M.: Anesth. and Analg. *51*:914, 1972
14. Fastner, Z. and Agoston, S.: Clinical Trials J. 7:254, 1970.
15. Sellick, B. A.: Der Anaesthesist *20*:76, 1971.
16. Baird, W. L. M.: Irish J. Med. Sc. (7th Series) *1*:559, 1968.
17. Nana, A., Cardan, E., and Leitersdorfer, T.: Anaesthesia *27*:154, 1972.
18. Levin, N. and Dillon, J.B.: Anesth. and Analg. *50*:808, 1971.

Organon

Organon Inc.
West Orange, N. J. 07052



NARCOTIC ANESTHESIA

- Despite many advantages, the use of opioids to supplement nitrous oxide anesthesia may be associated with significant postoperative depression.

NARCAN® (naloxone HCl)

- Narcan® in sufficient doses will antagonize opioid effects, including all degrees of respiratory depression and analgesia.
- The degree of narcotic antagonism exhibited by NARCAN® is dose dependent.

A recent study of surgical patients receiving narcotic-nitrous oxide anesthesia was undertaken to determine whether careful titration of naloxone would reverse post-operative narcotic depression and maintain a subjective level of analgesia.[1]

THE OBJECTIVES:

- Restore consciousness
- Reverse narcotic-induced respiratory depression as evidenced by $PaCO_2$
- Maintain *subjective* analgesia

THE METHOD:

- 12 unpremedicated patients received INNOVAR® (fentanyl/droperidol) 5-10 ml I.V. followed by thiopental for induction. Anesthesia was maintained with N_2O-O_2. Increments of 0.1 mg *fentanyl* were given I.V. every 10 minutes during surgery.

Following the procedure, naloxone (0.1 mg/ml) was given in 0.1 mg I.V. increments at 1 minute intervals until the patient was awake, lucid and had adequate tidal and minute volumes. Additional naloxone

1. Heisterkamp DV, Cohen PJ: *Anesth Analg* (Cleve) *53*:12-18, Jan-Feb 1974.

NARCAN® is an Endo registered U.S. trademark; U.S. Pat. 3,254,088.

was given I.V. as needed in the first 6 patients; a second group of 6 patients received supplemental naloxone I.M. 30 minutes after the initial I.V. dose.

- 11 patients received 10 mg *morphine* I.M., as well as secobarbital and atropine, 1½ hours preoperatively. Anesthesia was induced by 30 mg morphine given slowly I.V. followed by thiopental and was maintained by N_2O-O_2. Additional morphine was given in divided increments to total 1 mg/kg in the first hour. Further morphine was given as needed. For initial narcotic reversal, naloxone was given as above except at 2 minute intervals. Supplemental naloxone was given I.M. 30 minutes later.

THE RESULTS (fentanyl group):

- When fentanyl was used as the sole narcotic supplement during anesthesia, an I.M. dose of naloxone equal to half the I.V. reversal dose and given ½ hour later provided adequate narcotic reversal.

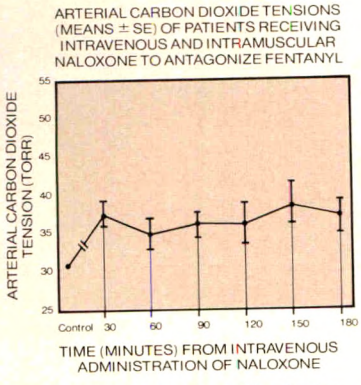


Fig. 1. Control and postoperative $PaCO_2$ in 6 patients receiving I.V. and I.M. naloxone following fentanyl.

THE RESULTS (morphine group):

- "After other narcotics, such as morphine, an I.M. dose of naloxone equal to the I.V. dose appears appropriate."

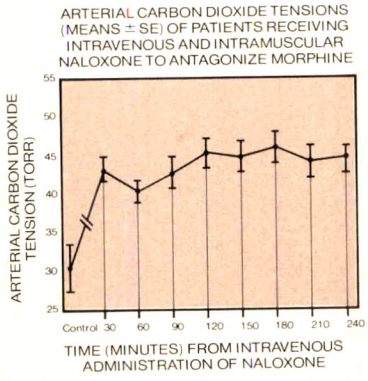


Fig. 2. Control and postoperative $PaCO_2$ in 11 patients receiving I.V. and I.M. naloxone following morphine.

THE CONCLUSIONS:

- "Naloxone provides fast, potent, and reliable antagonism to narcotic-induced respiratory depression."
- "By careful titration, this antagonism can be achieved while acceptable analgesia is maintained."
- "Both morphine and fentanyl groups had adequate analgesia, with only 2 patients [of total 21] requiring pain medication in the recovery room."

- **reverses all degrees of narcotic-induced respiratory depression**
- **does not cause narcotic-like effects**
- **does not augment non-narcotic depression**
- **acts rapidly—generally within 2 minutes following I.V. use and slightly less rapidly when given I.M.**
- **does not lead to tolerance**
- **does not produce psychotomimetic effects or pupillary constriction**
- **can be repeated if initial dose doesn't produce desired degree of narcotic reversal and improvement in respiratory function**
- **following satisfactory response patient should be observed closely and given repeat doses, if necessary, since the duration of action of some narcotics may exceed that of NARCAN®**

Please see next page for complete prescribing information.

Endo Laboratories, Inc.
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530
DUPONT

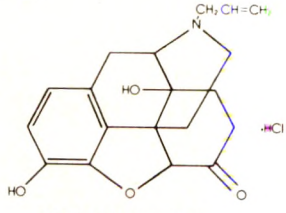
•restored consciousness
•reversed narcotic-induced respiratory depression
•maintained subjective analgesia

NARCAN®
(n lo -n- HCl)

can reverse narcotic-induced respiratory depression while maintaining subjective analgesia

NARCAN® (naloxone HCl)

DESCRIPTION NARCAN® (naloxone hydrochloride), a narcotic antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



NALOXONE HYDROCHLORIDE
(N-allyl-nor-oxymorphone HCl)

Naloxone hydrochloride occurs as slightly off-white crystals, and is soluble in water, slightly soluble in alcohol and practically insoluble in ether.

NARCAN® (naloxone hydrochloride) Injection is available in two concentrations, 0.02 mg and 0.4 mg of naloxone hydrochloride per ml. Each ml of either strength contains 8.5 mg of sodium chloride; and 2.0 mg of methylparaben and propylparaben as preservatives in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

ACTIONS NARCAN® (naloxone hydrochloride) is an essentially pure narcotic antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists; NARCAN® (naloxone hydrochloride) does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists it exhibits essentially no pharmacologic activity.

In the presence of physical dependence on narcotics NARCAN® (naloxone hydrochloride) will produce withdrawal symptoms; it has not been shown to produce tolerance nor to cause physical or psychological dependence.

When NARCAN® (naloxone hydrochloride) is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of NARCAN® (naloxone hydrochloride). Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of NARCAN® (naloxone hydrochloride), however, will also be dependent upon the amount, type and route of administration of the narcotic being antagonized.

INDICATIONS NARCAN® (naloxone hydrochloride) is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by natural and synthetic narcotics, propoxyphene and the narcotic-antagonist analgesic pentazocine.
NARCAN® (naloxone hydrochloride) is also indicated for the diagnosis of suspected acute opiate overdosage.

CONTRAINDICATIONS NARCAN® (naloxone hydrochloride) is contraindicated in patients known to be hypersensitive to it.

WARNINGS NARCAN® (naloxone hydrochloride) should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN® (naloxone hydrochloride) should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride).

NARCAN® (naloxone hydrochloride) is not effective against respiratory depression due to non-opioid drugs.

Usage in Pregnancy Safe use of NARCAN® (naloxone hydrochloride) during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or other embryotoxic effects (See ANIMAL PHARMACOLOGY AND TOXICOLOGY). However, NARCAN® (naloxone hydrochloride) should be administered to pregnant patients only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS In addition to NARCAN® (naloxone hydrochloride), other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

In an isolated report two patients with pre-existing ventricular irritability requiring lidocaine, and either isoproterenol or epinephrine for hypotension following cardiopulmonary bypass procedures, developed ventricular tachycardia or fibrillation when given NARCAN® (naloxone hydrochloride) I.V. at 9 and 14 hours, respectively, postoperatively for persistent unresponsiveness. Although a direct cause and effect relationship has not been established, NARCAN® (naloxone hydrochloride) should be used with caution in patients with cardiac irritability.

ADVERSE REACTIONS In rare instances nausea and vomiting have been reported in postoperative patients receiving NARCAN® (naloxone hydrochloride) in doses higher than that recommended; a cause and effect relationship has not been established.

DOSAGE AND ADMINISTRATION NARCAN® (naloxone hydrochloride) may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride) the patient should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary.

USAGE IN ADULTS Narcotic Overdose—Known or Suspected The usual initial adult dose is 0.4 mg (1 ml) NARCAN® (naloxone hydrochloride) administered I.V., I.M. or S.C. If the desired degree of counteraction and improvement in respiratory function is not obtained immediately following I.V. administration, it may be repeated intravenously at 2 to 3 minute intervals. Failure to obtain significant improvement after 2 or 3 doses suggests that the condition may be due partly or completely to other disease processes or non-opioid drugs.

Post Operative Narcotic Depression For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN® (naloxone hydrochloride) are usually sufficient. The dose of NARCAN® (naloxone hydrochloride) should be titrated according to the patient's response. Excessive dosage of NARCAN® (naloxone hydrochloride) may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or tachycardia.

For the initial reversal of respiratory depression, NARCAN® (naloxone hydrochloride) should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal i.e., adequate ventilation and alertness without significant pain or discomfort.

Repeat doses of NARCAN® (naloxone hydrochloride) may be required within one to two hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

USAGE IN CHILDREN Narcotic Overdose—Known or Suspected The usual initial child dose is 0.01 mg/kg body weight given I.V., I.M. or S.C. This dose may be repeated in accordance with the adult administration guideline. If necessary, NARCAN® (naloxone hydrochloride) can be diluted with sterile water for injection.

USAGE IN NEONATES Narcotic-induced depression The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines.

HOW SUPPLIED 0.4 mg/ml of NARCAN® (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration.

Available in 1 ml ampuls in boxes of 10 and 100.

0.02 mg/ml of NARCAN® (naloxone hydrochloride) NEONATAL INJECTION for intravenous, intramuscular and subcutaneous administration.

Available in 2 ml ampuls in boxes of 10 and 100 ampuls.

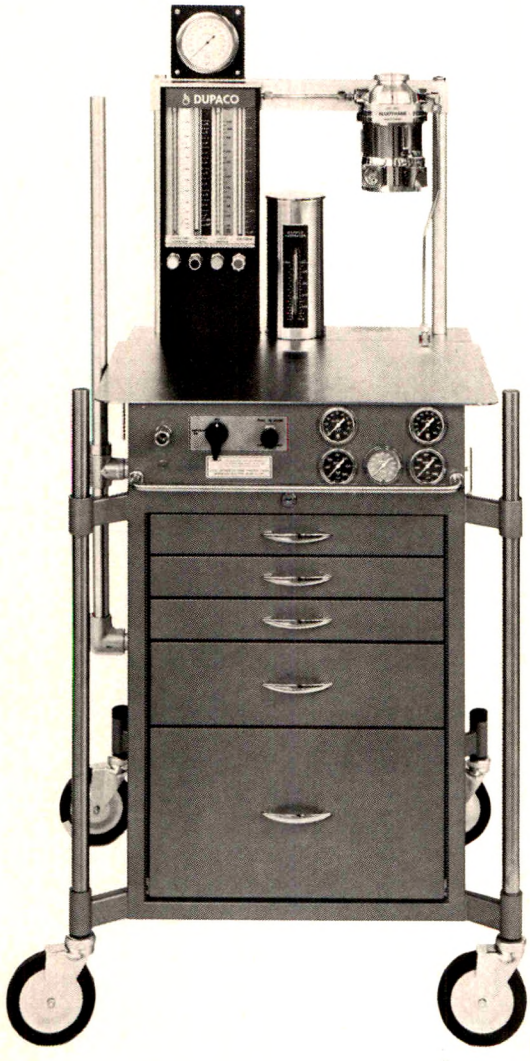
ANIMAL PHARMACOLOGY AND TOXICOLOGY In the mouse and rat the intravenous LD_{50} is 150 ±5 mg/kg and 109 ±4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the LD_{50} (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injections; no toxic effects were seen at 10 mg/kg/day for 3 weeks.

Reproductive studies including fertility, general reproductive performance, embryotoxicity, teratogenicity, and lactation did not show any abnormality in mice and rats at 10 mg/kg/day.

NARCAN® (naloxone hydrochloride) Ampuls
Stocked in Military Depot, NSN 6505-00-079-7867

Endo Laboratories, Inc.
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DUPONT



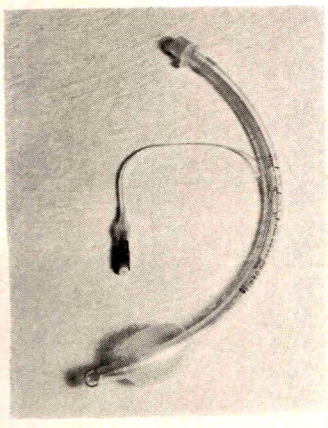
Now in your favorite color

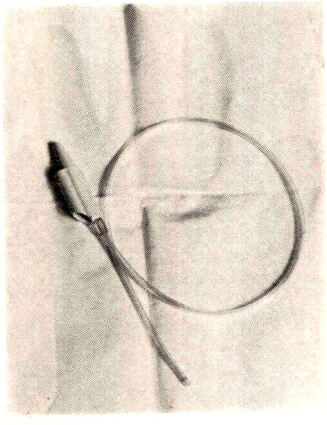
This is your opportunity to color coordinate your OR. Dupaco is offering the color of your choice on any Ventura or Palomar anesthesia apparatus at no extra charge. It's a machine you have to work with all day long... wouldn't it be nice if it was finished in your favorite color. Dupaco's Ventura and Palomar anesthesia apparatus is designed to meet the most challenging requirements of the profession. Now is the time to put a little color in your life! Write for our apparatus catalog and we will return it with a color certificate that will entitle you to any single color of your choice, at no extra charge.

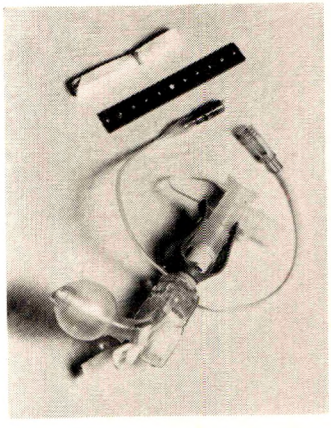
DUPACO
INCORPORATED

P.O. Box 98, San Marcos, CA 92069

National Catheter... we make lifelines.







hi-lo® tracheal tubes*

A high volume, low pressure cuffed endotracheal tube that inflates with a minimum of air pressure. Creates a no-leak seal, usually of less than 25 cm. H_2O; avoids trauma to the tracheal wall.

Soft and pliant tubes have a true murphy tip, intubate easily. Water clear, the tube fogs on exhalation, an instant monitor of patient respiratory function. May be used orally or nasally.

Other trademarks of NCC: **holdtite™, variform*, ventrol*, suture rib™, versi-cath*, maxi-flex & vac™, RAE™.**

*Covered under one or more of the following patents, U.S. Pat. No's 3,625,793, 3,605,750, 3,508,554, 3,610,242, and patents pending.

†University of Pittsburgh

Ncc satin-cath™* & gluv set

This sterile, disposable gluv set has met with overwhelming acceptance.

The GENTLE-FLO® catheter has a SATIN-SLIP SURFACE™ that provides smooth, non-binding insertion into an endotracheal tube.

The paperbacked glove slips on easily, fits either hand and is easily removed when suctioning is complete. The set also contains a waterproof receptacle. Pull the marked tabs and it opens and locks in position, ready to use for the receipt of sterile water. Equipped with VACTROL® connector, catheter suction may be simply regulated from full on to off.

Available with catheters in all popular sizes. Packaged in a sterile peel-back paper pouch—50 sets/box.

pitt*† trach speaking tube

This speaking tube permits tracheostomy patients to converse. The emotional benefits are obvious.

The hi-lo* cuff inflates easily to avoid tracheal damage. This possibility is further removed because the clear tubing permits convenient bronchoscopic observation of the tracheal wall. The auxiliary air supply tube is to be connected to a humidified air oxygen outlet to achieve a speaking air flow.

Equipped with Eross Safety Straps and removable spacers and adjustable collar, the trach tube is adaptable to fit any adult patient. The suction port, which may be locked, allows for suctioning of the patient without removing the respirator and introducing a flexible fiberoptic bronchoscope, thus avoiding delays during this critical period.

Manufactured with the precision medicine must demand.

national catheter corp.

A Mallinckrodt® COMPANY

Home of the Sheridan Line of Catheters argyle, new york 12809

ANECTINE®
(succinylcholine chloride)
For controlled muscle relaxation adjunctive to anesthesia:

FLO-PACK® for prolonged relaxation

- instant-mix sterile powder interfaces with all major parenteral systems (vacuum or nonvacuum)
- each unit complete—no needle or syringe needed
- retains potency indefinitely
- no refrigeration required
- unbreakable, sterile plastic injection units of 500 and 1,000 mg

INJECTION for short-term relaxation

- a product of choice for intubation and other short procedures
- unique square bottle and bright yellow label for positive identification
- ready for immediate use
- 20 mg per cc . . . in 10 cc multidose vials
- flip-top cap for easy opening
- single or multiple use

ANECTINE®
(succinylcholine chloride)
THE LONG AND SHORT of surgical muscle relaxation

THIS DRUG SHOULD BE USED ONLY BY INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS AND HAZARDS.

DESCRIPTION: Anectine brand Succinylcholine Chloride is an ultra short-acting depolarizing type muscle relaxant. Chemically it is a di-quaternary base consisting of the di-chloride salt of the di-choline ester of succinic acid. It is a white, odorless, slightly bitter powder and very soluble in water. The drug is unstable with alkaline solutions, but relatively stable in acid solutions depending upon the concentration of the solution and the storage temperature. While solutions of succinylcholine chloride are sterilized by autoclaving, they should, nevertheless, be stored under refrigeration to preserve their potency.

INDICATIONS: Succinylcholine chloride is indicated as an adjunct to anesthesia to induce skeletal muscle relaxation. It may be employed to reduce the intensity of muscle contractions of pharmacologically or electrically induced convulsions.

CONTRAINDICATIONS: Succinylcholine is contraindicated for persons with a known hypersensitivity to the drug.

WARNINGS:

WARNING: SUCCINYLCHOLINE SHOULD BE USED ONLY BY THOSE SKILLED IN THE MANAGEMENT OF ARTIFICIAL RESPIRATION AND ONLY WHEN FACILITIES ARE INSTANTLY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND FOR PROVIDING ADEQUATE VENTILATION OF THE PATIENT, INCLUDING THE ADMINISTRATION OF OXYGEN UNDER POSITIVE PRESSURE AND THE ELIMINATION OF CARBON DIOXIDE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR TO CONTROL RESPIRATION.

Succinylcholine should not be mixed with short-acting barbiturates in the same syringe, or administered simultaneously during intravenous infusion through the same needle. Solutions of succinylcholine have an acid pH whereas those of barbiturates are alkaline in reaction. Depending upon the resultant pH of a mixture of solutions of these drugs, either free barbituric acid may be precipitated or succinylcholine hydrolyzed.

Usage in Pregnancy. The safe use of succinylcholine has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

PRECAUTIONS: Low levels of, or abnormal variants of plasma cholinesterase may be associated with prolonged respiratory depression or apnea following the use of succinylcholine. Low levels of plasma cholinesterase may occur in patients with severe liver disease or cirrhosis, severe anemia, malnutrition, severe dehydration, changes in body temperature, exposure to neurotoxic insecticides or those receiving antimalarial drugs. Succinylcholine should be administered with extreme care to such patients and dosage should be minimal. If low plasma cholinesterase activity is suspected, a small test dose of from 5 to 10 mg of succinylcholine may be administered, or relaxation may be produced by the cautious administration of a 0.1% solution of the drug by intravenous drip. Drugs which either inhibit plasma cholinesterase, such as neostigmine or phospholine iodide, or compete with succinylcholine for the enzyme, as does intravenous procaine, should not be given concurrently with succinylcholine.

Succinylcholine should be administered with great caution to patients with severe burns, those recovering from severe trauma, those suffering from electrolyte imbalance, those receiving quinidine, those who have been digitalized recently or who may have digitalis toxicity as serious cardiac arrhythmias or cardiac arrest may result. Great caution should be observed also in patients with pre-existing hyperkalemia or who are paraplegic, have suffered spinal neuraxis injury, or have degenerative or dystrophic neuromuscular disease, as such patients tend to become severely hyperkalemic when succinylcholine is given.

When succinylcholine is given over a prolonged period of time, the characteristic depolarization block of the myoneural junction may change to a non-depolarizing block which results in prolonged respiratory depression or apnea. Under such circumstances, small repeated doses of neostigmine may possibly act as an antagonist. A peripheral nerve stimulator (e.g., the Wellcome Peripheral Nerve Stimulator) may be used to ascertain the type of neuromuscular blockade. If a depolarization block is present both fast (tetanic) and slow (twitch) rates of nerve stimulation are well sustained, and post-tetanic facilitation is absent. If a non-depolarizing block is present there is post-tetanic facilitation and "fade" of successive stimuli on both fast (tetanic) and slow (twitch) rates of nerve stimulation.

Succinylcholine should be used with caution during ocular surgery and in patients with glaucoma. The drug should be employed with caution in patients with fractures or muscle spasm as the muscle fasciculations may cause additional trauma. Muscle fasciculations and hyperkalemia may be reduced by administering a small dose of a non-depolarizing relaxant. If other relaxants are to be used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered.

During the past few years, reports have called attention to a fulminant syndrome, malignant hyperthermia, observed during anesthesia. Its etiology is not fully understood. Malignant hyperthermia occurs in genetically prone individuals of all ages and both sexes receiving potent anesthetics such as halothane, methoxyfluothane, cyclopropane and diethyl ether. It appears to develop irrespective of the concomitant use of a muscle relaxant, but may be triggered by succinylcholine. Because of the seriousness of this syndrome and the need for early effective treatment of the patient, it is suggested that the continuous monitoring of the temperature will serve as an aid to the early recognition of malignant hyperthermia.

ADVERSE REACTIONS: Adverse reactions consist primarily of an extension of the drug's pharmacological actions. Profound and prolonged muscle relaxation may occur, resulting in respiratory depression to the point of apnea. Hypersensitivity to the drug may exist in rare instances.

The following adverse reactions have been reported: bradycardia, tachycardia, hypertension, hypotension, arrhythmias, cardiac arrest, prolonged respiratory depression or apnea, hyperthermia, increased intraocular pressure, muscle fasciculation, postoperative muscle pain, myoglobinemia and excessive salivation.

MANAGEMENT OF ADVERSE REACTIONS: Apnea or prolonged muscle paralysis should be treated with controlled respiration.

The use of neostigmine to reverse a non-depolarization block is a medical decision which must be made upon the basis of the individual clinical pharmacology and the experience and judgment of the clinician. When neostigmine is used atropine should also be administered.

SUPPLIED: Injection, Multi-dose vials, 20 mg cc, 10 cc, boxes of 12 vials. Flo-Pack® Sterile Powder 500 mg and 1,000 mg, boxes of 12.

Complete literature available on request from Professional Services Dept. PML.

Wellcome
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

new flexible Fiber Optic

Laryngoscope

direct vision for difficult intubations

The first flexible fiberscope specifically for endotracheal intubations.

Portable, and with its own integral lighting system, the Flexible Fiber Optic Laryngoscope is inserted into the trachea under direct vision.

The articulating end-tip enables it to be directed into position for passage through the vocal cords. The scope then acts as a guide over which the endotracheal tube is passed.

When intubation is achieved, the scope is withdrawn leaving the tube in place.

The complete Flexible Fiber Optic Laryngoscope includes a 49 cm. flexible length, battery handle, 2 C cells, adjustable illumination, spare lamp and a special, foam-lined carrying case.

ANECTINE®
(succinylcholine chloride)
THE LONG AND SHORT of surgical muscle relaxation

THIS DRUG SHOULD BE USED ONLY BY INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS AND HAZARDS.

DESCRIPTION: Anectine brand Succinylcholine Chloride is an ultra short-acting depolarizing type muscle relaxant. Chemically it is a di-quaternary base consisting of the di-chloride salt of the di-choline ester of succinic acid. It is a white, odorless, slightly bitter powder and very soluble in water. The drug is unstable with alkaline solutions, but relatively stable in acid solutions depending upon the concentration of the solution and the storage temperature. While solutions of succinylcholine chloride are sterilized by autoclaving, they should, nevertheless, be stored under refrigeration to preserve their potency.

INDICATIONS: Succinylcholine chloride is indicated as an adjunct to anesthesia to induce skeletal muscle relaxation. It may be employed to reduce the intensity of muscle contractions of pharmacologically or electrically induced convulsions.

CONTRAINDICATIONS: Succinylcholine is contraindicated for persons with a known hypersensitivity to the drug.

WARNINGS:

WARNING: SUCCINYLCHOLINE SHOULD BE USED ONLY BY THOSE SKILLED IN THE MANAGEMENT OF ARTIFICIAL RESPIRATION AND ONLY WHEN FACILITIES ARE INSTANTLY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND FOR PROVIDING ADEQUATE VENTILATION OF THE PATIENT, INCLUDING THE ADMINISTRATION OF OXYGEN UNDER POSITIVE PRESSURE AND THE ELIMINATION OF CARBON DIOXIDE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR TO CONTROL RESPIRATION.

Succinylcholine should not be mixed with short-acting barbiturates in the same syringe, or administered simultaneously during intravenous infusion through the same needle. Solutions of succinylcholine have an acid pH whereas those of barbiturates are alkaline in reaction. Depending upon the resultant pH of a mixture of solutions of these drugs, either free barbituric acid may be precipitated or succinylcholine hydrolyzed.

Usage in Pregnancy. The safe use of succinylcholine has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

PRECAUTIONS: Low levels of, or abnormal variants of plasma cholinesterase may be associated with prolonged respiratory depression or apnea following the use of succinylcholine. Low levels of plasma cholinesterase may occur in patients with severe liver disease or cirrhosis, severe anemia, malnutrition, severe dehydration, changes in body temperature, exposure to neurotoxic insecticides or those receiving antimalarial drugs. Succinylcholine should be administered with extreme care to such patients and dosage should be minimal. If low plasma cholinesterase activity is suspected, a small test dose of from 5 to 10 mg of succinylcholine may be administered, or relaxation may be produced by the cautious administration of a 0.1% solution of the drug by intravenous drip. Drugs which either inhibit plasma cholinesterase, such as neostigmine or phospholine iodide, or compete with succinylcholine for the enzyme, as does intravenous procaine, should not be given concurrently with succinylcholine.

Succinylcholine should be administered with great caution to patients with severe burns, those recovering from severe trauma, those suffering from electrolyte imbalance, those receiving quinidine, those who have been digitalized recently or who may have digitalis toxicity as serious cardiac arrhythmias or cardiac arrest may result. Great caution should be observed also in patients with pre-existing hyperkalemia or who are paraplegic, have suffered spinal neuraxis injury, or have degenerative or dystrophic neuromuscular disease, as such patients tend to become severely hyperkalemic when succinylcholine is given.

When succinylcholine is given over a prolonged period of time, the characteristic depolarization block of the myoneural junction may change to a non-depolarizing block which results in prolonged respiratory depression or apnea. Under such circumstances, small repeated doses of neostigmine may possibly act as an antagonist. A peripheral nerve stimulator (e.g., the Wellcome Peripheral Nerve Stimulator) may be used to ascertain the type of neuromuscular blockade. If a depolarization block is present both fast (tetanic) and slow (twitch) rates of nerve stimulation are well sustained, and post-tetanic facilitation is absent. If a non-depolarizing block is present there is post-tetanic facilitation and "fade" of successive stimuli on both fast (tetanic) and slow (twitch) rates of nerve stimulation.

Succinylcholine should be used with caution during ocular surgery and in patients with glaucoma. The drug should be employed with caution in patients with fractures or muscle spasm as the muscle fasciculations may cause additional trauma. Muscle fasciculations and hyperkalemia may be reduced by administering a small dose of a non-depolarizing relaxant. If other relaxants are to be used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered.

During the past few years, reports have called attention to a fulminant syndrome, malignant hyperthermia, observed during anesthesia. Its etiology is not fully understood. Malignant hyperthermia occurs in genetically prone individuals of all ages and both sexes receiving potent anesthetics such as halothane, methoxyfluothane, cyclopropane and diethyl ether. It appears to develop irrespective of the concomitant use of a muscle relaxant, but may be triggered by succinylcholine. Because of the seriousness of this syndrome and the need for early effective treatment of the patient, it is suggested that the continuous monitoring of the temperature will serve as an aid to the early recognition of malignant hyperthermia.

ADVERSE REACTIONS: Adverse reactions consist primarily of an extension of the drug's pharmacological actions. Profound and prolonged muscle relaxation may occur, resulting in respiratory depression to the point of apnea. Hypersensitivity to the drug may exist in rare instances.

The following adverse reactions have been reported: bradycardia, tachycardia, hypertension, hypotension, arrhythmias, cardiac arrest, prolonged respiratory depression or apnea, hyperthermia, increased intraocular pressure, muscle fasciculation, postoperative muscle pain, myoglobinemia and excessive salivation.

MANAGEMENT OF ADVERSE REACTIONS: Apnea or prolonged muscle paralysis should be treated with controlled respiration.

The use of neostigmine to reverse a non-depolarization block is a medical decision which must be made upon the basis of the individual clinical pharmacology and the experience and judgment of the clinician. When neostigmine is used atropine should also be administered.

SUPPLIED: Injection, Multi-dose vials, 20 mg cc, 10 cc, boxes of 12 vials. Flo-Pack® Sterile Powder 500 mg and 1,000 mg, boxes of 12.

Complete literature available on request from Professional Services Dept. PML.

Wellcome
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

new flexible Fiber Optic

Laryngoscope

direct vision for difficult intubations

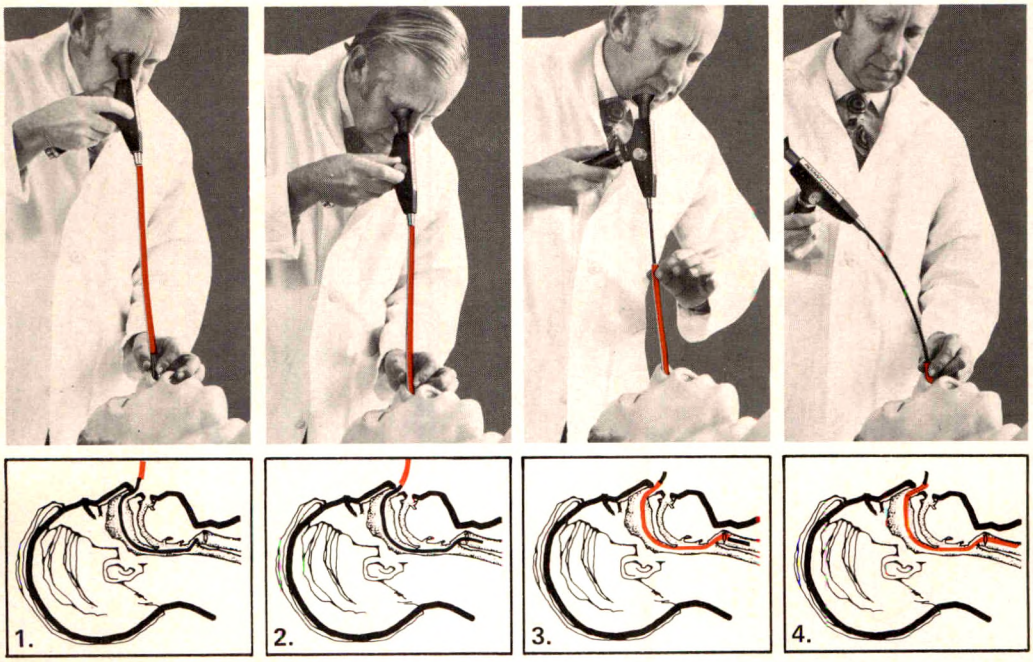
The first flexible fiberscope specifically for endotracheal intubations.

Portable, and with its own integral lighting system, the Flexible Fiber Optic Laryngoscope is inserted into the trachea under direct vision.

The articulating end-tip enables it to be directed into position for passage through the vocal cords. The scope then acts as a guide over which the endotracheal tube is passed.

When intubation is achieved, the scope is withdrawn leaving the tube in place.

The complete Flexible Fiber Optic Laryngoscope includes a 49 cm. flexible length, battery handle, 2 C cells, adjustable illumination, spare lamp and a special, foam-lined carrying case.



integral lighting, plus fiber optics forever eliminate "blind" intubations

1. Pass the flexible length through an endotracheal tube. The right hand controls end-tip deflection. The left hand introduces the scope through the nose, and advances it along the posterior wall of the pharynx and beyond the epiglottis.

Deflect the end-tip to see the larynx . . .

2. and pass it through the cords, into the trachea to a depth of about 5 cm.

The scope provides a clear, direct view of the internal anatomy as it travels along the respiratory tract.

3. When the end-tip is well in place within the trachea, simply advance the endotracheal tube. The scope acts as a stylet for the tube, making proper intubation a virtual certainty.

4. Remove the scope when intubation is completed.

Please rush ☐ product literature, ☐ research article reprints.

☐ I am interested also in a demonstration of the AO Flexible Fiberoptic Laryngoscope.

Name _____

Title _____

Representing _____

Street _____

City, State, Zip _____

AO® American Optical

MEDICAL DIVISION
Crosby Drive,
Bedford, MA 01730
617 275-0500

PLAN AHEAD

51ST CONGRESS

MARCH 6-10, 1977

International Anesthesia Research Society

DIPLOMAT RESORT AND COUNTRY CLUBS
HOLLYWOOD, FLORIDA

CALL FOR PAPERS

August 2, 1976—Deadline for submission of titles and abstracts. Application forms will be available May 1, 1976 from: John T. Martin, M.D., Chairman, Program Committee, Medical College of Ohio at Toledo, P. O. Box 6190, Toledo, Ohio 43614.

A Technic of General Anesthesia for Blepharoplasty and Rhytidectomy

HERZL KATZ, M.D.*
ROY C. MACHIDA, M.D.†
D. GARETH WOOTTON, M.D.†
ROBERT AMONIC, M.D.†

A series of 66 consecutive cases of blepharoplasty and rhytidectomy are reported, 60 of which were performed with a general anesthesia technic utilizing local anesthesia with epinephrine, in association with enflurane inhalation delivered via bilateral nasopharyngeal airways (BNPA). Six cases were not suitable candidates for the technic because of physical status or for anatomic reasons. The technic has the advantage of providing airway control without tracheal intubation, light depth of anesthesia, compatibility with epinephrine, and highly acceptable limits of intraoperative bleeding and postoperative hematoma.

LOCAL anesthesia with epinephrine and preoperative basal sedation is used in the majority of blepharoplasties and rhytidectomies. Frequently, however, because of patient restlessness during the lengthy procedure, IV hypnotic or narcotic supplementation is needed, with the associated danger of hypoventilation or loss of airway control in a poorly accessible field.

There appears to be reluctance to routinely use general endotracheal anesthesia because of the added anesthesia risks and dangers involved, and the concern about possible increased incidence of hematomas under the extensive skin flaps. Many patients, however, are concerned about being awake and suffering discomfort during the long procedure, which often is 3 to 4 hours in duration.

An optimum technic of general anesthesia for blepharoplasty and rhytidectomy should provide the following:

(1) Maintenance of an adequate airway
(2) Controllable light levels of anesthesia
(3) Anesthetic agents compatible with epinephrine
(4) Acceptable intraoperative blood loss
(5) Minimal postoperative hematoma formation
(6) Minimal bucking and straining
(7) Smooth emergence from anesthesia
(8) Minimal postanesthetic morbidity

In our hands, a technic utilizing local anesthesia with epinephrine in association with enflurane inhalation delivered through bilateral nasopharyngeal airways (BNPA) has proved successful. We report a series of 66 consecutive cases of combined blepharoplasty and rhytidectomy, of which 60 were judged suitable for this anesthetic technic.

*Clinical Instructor, Department of Anesthesiology, University of California, Los Angeles, California.
†Clinical Instructor in Surgery, Division of Plastic Surgery, University of California, Los Angeles, California.
Reprint requests to: Herzl Katz, M.D., 1316 Capri Drive, Pacific Palisades, California 90272.

Paper received: 4/14/75
Accepted for publication: 8/13/75

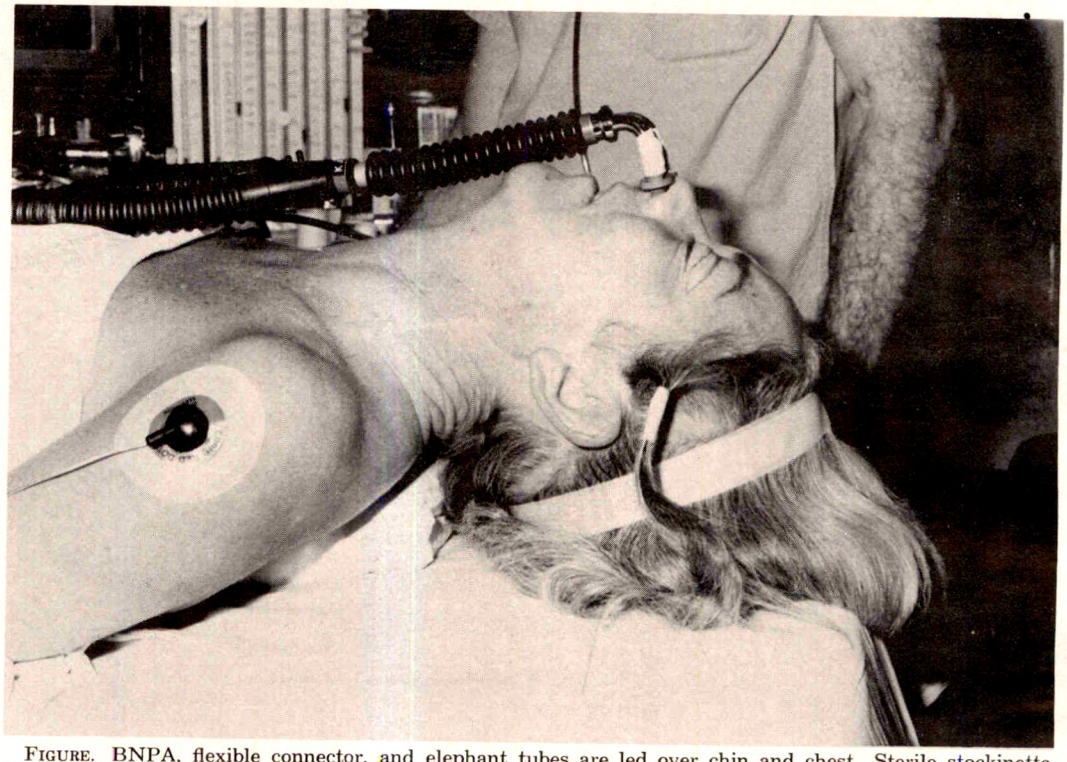


FIGURE. BNPA, flexible connector, and elephant tubes are led over chin and chest. Sterile stockinette is placed over the connector.

PROCEDURE

The BNPA technic was first described in 1969 by Elam and associates.[1,2] Patients are monitored with precordial stethoscope, BP cuff, and continuous ECG. After an induction dose of barbiturate, 2 well-lubricated 26 French Rusch red-rubber nasopharyngeal airways with adapter preattached are gently and cautiously advanced through the nares and choanae and directed posteriorly and inferiorly along the floor of the nasopharynx. When advanced completely, the airway ends will be positioned just below the tip of the epiglottis. The anesthesia machine and anesthesiologist can be positioned at either side of the patient (figure).

A folded sheet or sandbag is placed longitudinally under the patient's back, for adequate neck extension; flexion or incomplete extension may cause the BNPA to kink and obstruct the airway. The adequacy of the airway can now be tested by turning the head from side to side and observing bag movement as an index of obstruction.

In approximately 90% of patients with the BNPA technic, it is possible to assist or control respirations as long as the glottis remains patent, because the tongue and soft pharyngeal structures collapse to form a seal about the tubes. Elam[1] demonstrated that the esophageal opening pressure of 15 to 25 cm H_2O exceeds the 10 to 20 cm H_2O bag pressure which will produce excess oral gas "pop-off," so that positive bag pressure can be applied and overflow gases vented orally with little danger of inflating the stomach.

Maintenance flows of N_2O-O_2 (2 L:2 L) and 1.0 to 2.5% enflurane are delivered; the actual concentration inhaled by the patient is less than this because of some air-mixing in the oropharynx. The surgeon infiltrates initially with a suitable local agent with epinephrine to a maximum of 100 μg, an amount safely compatible with enflurane; local epinephrine is injected again at appropriate intervals.[3] Systolic pressures are usually maintained in the 80 to 100 torr range.

Spontaneous respirations are usually adequate in volume, as measured by Vortex respirometer, and are assisted at intervals. If gross leaks are present, vaseline gauze may be used to seal the nares about the tubes. Constant monitoring of bag movement as evidence of airway patency is essential.

The patient is taken to the recovery room with the BNPA in place. Airways are well

tolerated, without bucking, until the patient is awake, usually within 15 minutes of arrival.

THE SERIES

Our series included 66 consecutive women who underwent both blepharoplasty and rhytidectomy. All patients were seen preoperatively and postoperatively, and 6 patients were omitted from the study as unsuitable candidates for the BNPA technic. Of these, 2 had histories of previous nasal surgery, one had moderate obstructive respiratory disease, and 3 had short, receding chins and limited head extension, suggesting that airway maintenance with BNPA would be difficult. We elected to intubate this group orotracheally immediately on induction.

Patients ranged in age from 43 to 67 years (mean 56); 88% were in the 43 to 64 age range. Fifty-six patients were ASA class I; 4 were in class II. All procedures were performed by the same group of physicians. Blood loss was estimated visually from drapes and sponges.

RESULTS

During our early experience, the level of anesthesia lightened precipitously and laryngeal spasm occurred in 4 cases. It was necessary to partially undrape the field and intubate orotracheally; an endotracheal tube should always be available for such an emergency. However, with more experience, this has not occurred in our last 35 consecutive cases.

Total anesthesia time ranged from 2½ to 5 hours; 83% of the cases were 3 to 4 hours in duration. We have had no episodes of gastric inflation, silent regurgitation, or aspiration clinically demonstrable during these lengthy procedures. Blood loss was estimated between 125 and 600 ml (mean 285 ml).

There were no hypotensive episodes, and no transfusions were required (table). The postoperative hematoma rate was 3.3% (2 patients); only one of these was returned to the operating suite for evacuation of extensive clots. Patients were uniformly grateful that they had been anesthetized for the procedure.

TABLE
Complications and Morbidity

	Number	Percent
Intubated intraoperatively	4	7
Hypotension	0	0
Excitement emergence	4	7
Epistaxis	0	0
Postoperative hematomas	2	3.3
Nausea	5	8
Vomiting	7	12
Headache	6	10

DISCUSSION

We do not use the BNPA technic in patients with a history of previous nasal surgery, severe nasal obstruction, nasal polyps or allergies, or patients with anatomically hazardous head and neck configurations, such as short or receding chins, bull-neck, or limited head extension, preferring to intubate these patients immediately on induction. Though we are well aware of the potential hazard, we have not had any problems with gastric inflation or silent regurgitation. As a rule, patients who desire this procedure are in good general health, ASA class I or II, although many are in the sixties age group. We do not accept ASA class III patients for this highly elective procedure.

As mentioned, the breathing bag must be watched *constantly* for evidence of airway obstruction and adequacy of ventilation volume. The surgeon must be cooperative in maintaining proper extension of the head. When necessary, the head must be turned gently to avoid dislodging the airways. Should there be any airway difficulties, the surgeon must be prepared to stand aside immediately so that the anesthesiologist can assess the problem and intubate if required. Close cooperation between surgeon and anesthesiologist is a necessity.

ACKNOWLEDGMENT

The authors thank Mrs. Nancy Brault and Mrs. Eleanor Rondelle, librarians, Saint John's Hospital; Mrs. Barbara Rydgren, Medical Records Department; and the Misses Rhoda Weiss and Glenna Webb for secretarial help.

REFERENCES

1. Elam JO, Titel JH, Feingold A, et al: Simplified airway management during anesthesia or resuscitation: a binasal pharyngeal system. Anesth & Analg 48:307-316, 1969

2. Weisman H, Weis TW, Elam JO, et al: Use of double nasopharyngeal airways in anesthesia. Anesth & Analg 48:356-361, 1969

3. Lippmann M, Reisner LS: Epinephrine injection with enflurane anesthesia: incidence of cardiac arrhythmias. Anesth & Analg 53:886-889, 1974

Cardiovascular Dynamics After Large Doses of Fentanyl and Fentanyl Plus N_2O in the Dog

WEN-SHIN LIU, MD*
ARUN V. BIDWAI, MD†
THEODORE H. STANLEY, MD‡
JESUS ISERN-AMARAL, MD§
Salt Lake City, Utah‖

The effects of large doses of fentanyl (0.05 to 2 mg/kg) and fentanyl plus N_2O on cardiovascular dynamics were determined in 10 unpremedicated dogs breathing 100% O_2. Using computer analysis of the central aortic pulse-pressure curve, stroke volume (SV), cardiac output, heart rate (HR), peripheral vascular resistance (PVR), and systolic, diastolic, and mean arterial blood pressures (BP) were determined while fentanyl was being given at a rate of 0.3 to 0.44 mg/min. Fentanyl caused a dose-related decrease in HR, which was significant at 0.05 mg/kg. Cardiac output, PVR, and systolic, diastolic, and mean arterial BP were also decreased and SV increased. The latter changes became significant at 0.1 mg/kg for diastolic BP; 0.15 mg/kg for cardiac output and mean BP; 0.25 mg/kg for SV and systolic BP; and at 1.25 mg/kg for peripheral vascular resistance. Addition of N_2O after fentanyl did not significantly change any parameter, although SV, cardiac output, and HR were usually increased and PVR decreased.

These data demonstrate that, while large doses of fentanyl or fentanyl plus N_2O do alter cardiovascular dynamics in dogs, the changes appear to be less profound than those produced by equianalgesic doses of morphine. Our findings suggest that large doses of fentanyl-O_2 may be an attractive alternative to morphine-O_2 anesthesia in critically ill patients.

FENTANYL, 1-(2-phenethyl)-4-(n-propionylanilino)-piperidine, in doses of 0.02 mg/kg, has little effect on left ventricular dynamics in the neurally intact, blood-perfused dog heart.[1,2] In man, 10 μg/kg of fentanyl significantly increases stroke volume (SV) and cardiac index (CI).[3] These data suggest that large doses of fentanyl and O_2 may represent an attractive alternative to morphine and O_2 anesthesia for critically ill patients. However, while fentanyl has approximately 130 to 180 times the analgesic potency of morphine,[4,5] its amnesic properties have not been established. It is, therefore, difficult to know what dosages will be required for complete anesthesia in man, and what the cardiovascular effects of these doses will be if fentanyl is used as the sole anesthetic. This study was undertaken to investigate the cardiovascular effects of a range of high doses of fentanyl alone and fentanyl plus N_2O in the dog.

METHODS

Ten fasted, unpremedicated mongrel dogs, average weight 17 kg (range 15 to 22 kg),

*Fellow in Anesthesiology and Artificial Organs.

†Staff Anesthesiologist, Holy Cross Hospital; Clinical Instructor in Anesthesiology, University of Utah.

‡Associate Professor of Anesthesiology and Assistant Research Professor of Surgery.

§Fellow in Anesthesiology and Artificial Organs.

‖Department of Anesthesiology and Division of Artificial Organs, University of Utah College of Medicine, Salt Lake City, Utah 84132.

This study was supported in part by a grant from McNeil Laboratories, Fort Washington, Pennsylvania.

Paper received: 7/18/75
Accepted for publication: 7/29/75

served as experimental subjects. Each animal had an IV infusion of lactated Ringer's solution started in a foreleg prior to anesthesia, was induced and intubated after 5 to 10 mg/kg of sodium thiopental and 2 mg/kg of succinylcholine, and was ventilated with 100% O_2 at tidal volumes of 5 to 12 ml/kg with a volume-limited respirator. Respirations were controlled to maintain $Paco_2$ between 30 and 35 torr, as measured in aortic blood every 15 minutes.

Immediately after intubation, a Teflon catheter was implanted in the femoral artery through a small groin incision and threaded 20 to 35 cm to the central aorta. The aortic pressure catheter was attached via a Statham P23 Db arterial pressure transducer to a central digital computer substation (Tektronix® memory oscilloscope) in the laboratory. Warner's method of analyzing the central aortic pulse-pressure curve was used to determine cardiac output, SV, arterial BP and peripheral vascular resistance (PVR), and heart rate (HR).[6] Occasionally, additional 1 to 5 mg/kg doses of sodium thiopental and 1 mg/kg doses of succinylcholine were required to maintain anesthesia until the aortic catheter was in place. Following placement of ECG leads on the extremities and a 15-minute equilibration period, control (pre-fentanyl) measurements of HR, SV, cardiac output, SVR, and systolic, diastolic, and mean arterial BP were obtained. Fentanyl (0.06 mg/ml) was then administered IV as a continuous infusion at a rate of 0.3 to 0.44 mg/min in lactated Ringer's solution. Additional data were obtained following infusion of 0.05, 0.1, 0.15, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, and 2 mg/kg of the drug. The inspired gases were then changed to 50% N_2O in O_2, and after a 20-minute equilibration period, a final set of data was taken. Data were analyzed for statistical significance using Student's paired *t*-test.

RESULTS

Changes in cardiovascular dynamics versus dose of fentanyl are given in the table. Fentanyl caused a dose-related increase in SV and decrease in HR, systolic, diastolic, and mean arterial BP, and peripheral vascular resistance. While HR was significantly decreased after 0.05 mg/kg of fentanyl, it took 0.1 to 0.25 mg/kg to produce significant changes in SV and arterial pressures and 1.25 mg/kg to significantly alter peripheral vascular resistance. Cardiac output was also reduced by fentanyl. The major proportion of the reduction occurred prior to 0.25 mg/kg. Additional fentanyl had little further effect on cardiac output.

Addition of 50% N_2O after 2 mg/kg of fentanyl did not significantly alter any cardiovascular parameter studied. However, most animals had small increases in HR, SV, and cardiac output and decreases in peripheral vascular resistance. In 3 dogs, addition of N_2O increased cardiac output by more than 500 ml/min. No dog experienced any arrhythmia either during fentanyl administration or after the addition of N_2O to the inspired mixture of gases.

DISCUSSION

Large doses of IV morphine (0.5 to 3 mg/kg) plus O_2 has little effect on myocardial dynamics and has, therefore, become popular as an anesthetic technic for critically ill patients undergoing cardiac and other major operative procedures.[7,8] However, hypotension,[8,9] hypertension,[9] increased blood requirements,[10] antidiuresis,[11] and incomplete amnesia[8] have been demonstrated to be disadvantages of morphine-O_2 anesthesia. Fentanyl, a potent, short-acting synthetic narcotic, also produces no detectable cardiovascular depression in doses equianalgesic to anesthetic doses of morphine,[1-3] and possesses the additional advantages of not causing histamine release and being easily reversible with naloxone.[2]

While the combination of fentanyl and droperidol, a butyrophenone, is reputed to cause minimal changes in myocardial contractility[12] and cardiovascular dynamics[13] and has achieved clinical acceptance as an anesthetic for critically ill patients, recent data suggests that droperidol in clinically used dosages significantly impairs left ventricular function.[1] On the basis of the above, large doses of fentanyl, as the sole anesthetic, plus O_2 has been advocated and seems reasonable as an alternative anesthetic technic to morphine-O_2 for critically ill patients.[2] However, the amnesic qualities of doses of fentanyl that are equianalgesic to morphine are unknown.

A study in preoperative patients comparing fentanyl (0.5 mg) with an equianalgesic dose of meperidine (500 mg), a drug not noted for its amnesic actions, found that the former resulted in significantly less amnesia than the latter.[14] This suggests that extremely large doses of fentanyl may be required to achieve amnesia when used as the sole anesthetic.

TABLE

Cardiovascular Effects of Fentanyl and Fentanyl Plus 50% N_2O
(Mean ± SD)

	Control	Fentanyl (mg/kg) 0.05	0.1	0.15	0.25	0.5	0.75	1	1.25	1.5	1.75	2	2 + 50% N_2O
Cardiac output, L/min	3.5 ±1.0	3.0 ±0.9	2.7 ±1.0	2.4* ±0.9	2.4† ±0.8	2.3† ±0.7	2.2† ±0.9	2.3† ±0.7	2.4† ±0.6	2.3† ±0.7	2.3† ±0.9	2.2† ±0.6	2.6† ±0.8
SV, ml	29 ±9	29 ±6	31 ±8	29 ±9	35* ±8	38† ±7	39† ±8	40† ±6.5	41† ±7	40† ±7.5	41† ±8	42† ±7	44* ±7
HR, bpm	128 ±16	95* ±20	87† ±25	84† ±30	69‡ ±28	61‡ ±26	60‡ ±31	58‡ ±30	58‡ ±30	57‡ ±30	57‡ ±31	54‡ ±29	61‡ ±33
Peripheral resistance, PRU	196 ±22	199 ±23	176 ±45	179 ±29	165 ±36	153 ±35	145 ±40	138 ±32	130* ±29	137 ±41	128* ±35	128* ±39	113* ±40
BP, torr													
Systolic	164 ±18	144 ±26	142 ±30	140 ±36	138* ±28	135* ±28	128† ±27	129† ±26	127† ±29	129† ±31	127† ±32	122† ±35	122† ±38
Diastolic	109 ±20	91 ±26	81* ±35	73* ±26	70† ±35	58‡ ±30	49‡ ±25	47‡ ±26	45‡ ±25	48‡ ±28	44‡ ±26	40‡ ±27	38‡ ±28
Mean	132 ±16	113 ±18	107 ±33	104* ±34	99† ±31	91† ±26	83‡ ±22	81‡ ±25	79‡ ±22	82‡ ±24	79‡ ±26	75‡ ±26	68‡ ±36

*$p < 0.05$, Student's t-test, when compared to control values.

†$p < 0.01$, Student's t-test, when compared to control values.

‡$p < 0.001$, Student's t-test, when compared to control values.

Our present study of the cardiovascular effects of 0.05 to 2 mg/kg of fentanyl in unatropinized dogs demonstrates that these enormous doses of fentanyl are associated with significant decreases in HR, cardiac output, arterial BP, PVR, and increases in stroke volume. While most of the parameters measured were progressively changed by increasing fentanyl dosages, almost all the decrease in cardiac output had occurred by the time 0.15 mg/kg was given. Thereafter, further decreases in HR were approximately compensated by simultaneous decreases in PVR and increases in stroke volume. This maintained cardiac output relatively constant.

The greatest decrease in output in any of the animals was 53%, and no animal had a systolic arterial BP <89 torr at any time. Addition of 50% N_2O after 2 mg/kg of fentanyl, instead of producing cardiovascular depression as was expected, did not significantly change any cardiovascular parameter measured. Indeed, SV, cardiac output, and HR were usually increased by N_2O. These data suggest that enormous doses of fentanyl are at least as, and possibly more, benign on canine cardiovascular dynamics as comparable doses of morphine.

Both morphine and fentanyl significantly decrease peak developed tension and the maximum rates of tension development and relaxation in proportion to dose in isolated saline-perfused rat heart muscle.[5] However, neither has a significant effect on myocardial contractility in blood-perfused hearts.[1,2,15] Although a detailed comparison of the cardiovascular effects of a range of comparable doses of morphine and fentanyl in intact animals has not been published, Schmidt and Livingston[16] found that 1 mg/kg of morphine injected IV produced marked decreases in canine HR and arterial BP, which lasted for 10 minutes.

Gardocki and Yelnosky[4] found that comparable doses of fentanyl (0.005 mg/kg) have no effect on HR and arterial BP in dogs, and that 0.01 to 0.04 mg/kg of fentanyl produced 15 to 30% less reduction in arterial BP than did 1/3 the equianalgesic dose of morphine (0.5 to 2 mg/kg) in dogs. Our data in this study show that 2 mg/kg of fentanyl reduces systolic arterial BP an average of 26%. Schmidt and Livingston[16] found that approximately half of a comparable dose of morphine (200 mg/kg) resulted in complete cardiovascular collapse and death in dogs.

The most immediate cardiovascular change produced by fentanyl in this study was bradycardia, HR being reduced an average of 25% after 0.05 mg/kg and an average of 52% after 2 mg/kg. Gardocki and Yelnosky[4] demonstrated that bradycardia produced by 0.04 mg/kg of fentanyl in dogs can be significantly decreased by premedication with atropine (1 mg/kg IV) or surgical vagotomy. They also showed that fentanyl-induced bradycardia can be completely reversed, once produced, with 0.1 to 0.5 mg/kg of IV atropine. This was not investigated in the present study, but in another investigation (unpublished data) we have shown that the above doses of atropine, given either as premedication or after administration of 1 mg/kg of fentanyl, while not completely preventing or reversing bradycardia, will significantly decrease it. Atropine also reduced decreases in cardiac output and arterial BP.

It could be reasoned that fentanyl in the doses used in this study would produce greater cardiovascular depression in unstimulated supine man than in intubated, minimally anesthetized dogs already subjected to the stimulation of a groin incision. That our animals may have been under some sympathetic stimulation is suggested by the high mean cardiac output (3.5 L/min or 203 ml/kg/min versus a normal of 139 ml/kg/min)[17] HR and arterial pressures during the control period. On the other hand, starting with animals already under sympathetic stimulation may have magnified the depressant effects of fentanyl in our study. Indeed, the greatest decreases in heart rate (−25%), cardiac output (−17%) and arterial BP (−12 to 17%) occurred during administration of the first 0.05 mg/kg of fentanyl. Subsequent increments of the drug produced much less change. In fact, it took all the rest of the 1.95 mg/kg of fentanyl administered to duplicate the initial percentage decrease in heart rate.

The cardiovascular effects and amnesic qualities of such doses of fentanyl as were used in this study are unknown in man. Stoelting and coworkers[3] found that 0.01 mg/kg of fentanyl produced no significant changes in mean arterial BP, HR, cardiac index, SV, and peripheral arterial resistance in supine, preoperative patients with valvular heart disease premedicated with fentanyl and scopolamine. This dose of fentanyl is equianalgesic to 2 mg/kg of morphine in the mouse.[4] Unfortunately, the analgesic and amnesic qualities of fentanyl were not

evaluated in Stoelting's patients.[3] However, they did show that addition of 60% N_2O significantly reduced mean arterial pressure, cardiac index, and HR, and suggested that the CI and BP reductions were primarily due to a decrease in HR.

It is interesting that although the changes were not significant, 50% N_2O tended to increase HR and cardiac output in our dogs after 2 mg/kg of fentanyl. Why N_2O acts differently in the dog after large doses of fentanyl than it does in man with smaller doses is unclear at this time.

REFERENCES

1. Ostheimer GW, Shanahan EA, Guyton RA, et al: Effects of fentanyl and droperidol on canine left ventricular performance. Anesthesiology 42:288-291, 1975

2. Freye E: Cardiovascular effects of high dosages of fentanyl, meperidine and naloxone in dogs. Anesth & Analg 53:40-47, 1974

3. Stoelting RK, Gibbs PS, Creasser CW, et al: Hemodynamic and ventilatory responses to fentanyl, fentanyl-droperidol and nitrous oxide in patients with acquired valvular heart disease. Anesthesiology 42:319-324, 1975

4. Gardocki JF, Yelnosky J: A study of some of the pharmacologic actions of fentanyl citrate. Toxicol Appl Pharmacol 6:48-62, 1964

5. Goldberg AH, Padget CH: Comparative effects of morphine and fentanyl on isolated heart muscle. Anesth & Analg 48:978-982, 1969

6. Warner HR, Gardner FM, Toronoto AR: Computer-based monitoring of cardiovascular functions in postoperative patients. Circulation 38:68-74, 1968

7. Lowenstein E, Hallowell P, Levine FH, et al: Cardiovascular response to large doses of intravenous morphine in man. N Engl J Med 281:1389-1393, 1969

8. Lowenstein E: Morphine "anesthesia" — a perspective. Anesthesiology 35:563-565, 1971

9. Arens JF, Benbow BP, Ochsner JL, et al: Morphine anesthesia for aortocoronary bypass procedures. Anesth & Analg 51:901-909, 1972

10. Stanley TH, Gray NH, Isern-Amaral J: Comparison of blood requirements during morphine and halothane anesthesia for open-heart surgery. Anesthesiology 41:34-38, 1974

11. Mannheimer WH: The use of morphine and intravenous alcohol in the anesthetic management of open-heart surgery. South Med J 64:1125-1127, 1971

12. Dixon SH, Nolan SP, Stewart S, et al: Neuroleptanalgesia: effects of Innovar® on myocardial contractility, total peripheral vascular resistance, and capacitance. Anesth & Analg 49:331-335, 1970

13. Corssen G, Chodoff P, Domino EF, et al: Neuroleptanalgesia and anesthesia for open-heart surgery. Pharmacologic rationale and clinical experience. J Thorac Cardiovasc Surg 49:901-920, 1965

14. Mostert JW, Trudnowski RJ, Seniff AM, et al: Clinical comparison of fentanyl with meperidine. J Clin Pharmacol 8:382-391, 1968

15. Flacke W: Some actions of morphine cn the circulation (abstract). Fed Proc 24:613, 1965

16. Schmidt CF, Livingston AE: The action of morphine on the mammalian circulation. J Pharmacol Exp Ther 47:411-441, 1933

17. Prosser CL, Brown FA: Comparative Animal Physiology. Philadelphia, WB Saunders Company, 1961, pp 395-396

OXYGEN AND MYOCARDIAL INFARCTION SIZE Interventions that improve the balance between myocardial oxygen supply and demand may reduce the size of a myocardial infarction. The present investigation sought to determine the influence of O_2 administration on myocardial infarction size following coronary artery ligation in the dog. The average ST segment elevation was reduced and CPK release less following coronary artery ligation breathing 40% O_2 as compared with breathing 20% O_2. It was postulated that increased oxygen availability to ischemic areas constituted the mechanism by which 40% oxygen reduced acute ischemic injury. Breathing pure O_2 was not found to be more beneficial than 40% O_2. An FIO_2 of 0.4 may be appropriate in the treatment of patients with acute myocardial infarction. *(Maroko PR, Radvany P, Braunwald E et al: Reduction of infarct size by oxygen inhalation following acute coronary occlusion. Cir 52:360-368, 1975)*

Anesthetic Considerations in Diffuse Bleeding Diathesis of Uncertain Origin

F. Y. DALAL, FFARCS*
E. J. BENNETT, FFARCS†
E. M. GRUNDY, FFARCS‡
S. YOUNES, MD§
E. ORFEI, MD‖

This is a report of a case of a diffuse bleeding tendency in a pregnant woman who presented for emergency splenectomy with a tentative diagnosis of thrombotic thrombocytopenic purpura. The influence of multiple organ dysfunction in the selection of appropriate monitors and the anesthetic technic in such cases are complex.

A PATIENT for emergency surgery with bleeding diathesis is a major anesthetic problem. Disseminated intravascular coagulation (DIC) and thrombotic thrombocytopenic purpura (TTP) are examples of two such conditions. Following is a report of a patient with a bleeding diathesis, tentatively diagnosed as TTP on our clinical and hematologic findings. In TTP, the basic problem is multiple organ failure due to hyaline thrombus formation in the arterioles and capillaries.[1] Until recently, TTP was almost invariably fatal.[2] With the observation that splenectomy (in addition to massive doses of steroids, heparinization, and antiplatelet-aggregating drugs such as aspirin and dipyridamole) has improved the prognosis significantly, anesthesiologists can expect to be confronted more frequently with such patients.[3-5] On the other hand, patients with DIC may present for control of bleeding in certain obstetric emergencies such as abruptio placentae, prostatic surgery, or after brain, liver, or lung damage.[6-8] The anesthetic literature is devoid of any guidelines for the rational management of such patients and is the reason for this report.

CASE REPORT

A 22-year-old Caucasian woman was admitted to another hospital with a presumptive diagnosis of hemolytic anemia. After 5 days, she was transferred to Loyola University for evaluation and treatment and was found to be 20 weeks pregnant. A tentative diagnosis of TTP was entertained on the basis of low platelet count, hemolysis, changing mental status, fever, and hematuria. Examination revealed splenomegaly,

*Associate Professor, Department of Anesthesiology, Loyola University Stritch School of Medicine, Maywood, Illinois 60153.

†Professor, Department of Anesthesiology, Abraham Lincoln School of Medicine, University of Illinois, Chicago, Illinois.

‡Assistant Professor, Department of Anesthesiology, Abraham Lincoln School of Medicine, University of Illinois, Chicago, Illinois.

§Assistant Professor, Department of Anesthesiology, Loyola University Stritch School of Medicine.

‖Associate Professor of Pathology, Department of Pathology, Loyola University Stritch School of Medicine.

Paper received: 3/3/75
Accepted for publication: 8/4/75

TABLE
Laboratory Data
(Figures in parentheses are normal values)

	11/13	11/16	11/18	11/19	11/25
Hemoglobin (14 ± 2 mg %)	—	6.8	8.5	9.9	11.5
Hematocrit (42 ± 5%)	—	21.0	24.0	29.7	34.5
Reticulocytes (0.5-1.5%)	23.5	12.8	—	—	—
Platelets (200,000-400,000 cu m)	—	—	10,000	5,000	49,000
Coagulation profile and plasminogen system normal					
BUN (9-22 mg/dl)	—	11.0	17.3	49.0	17.0
Bilirubin T (0.2-1.5 mg/dl)	—	1.5	2.2	3.1	—
Electrolytes: Na^+, 145; K^+, 5; Cl^-, 104; CO_2, 19.4; glucose, 95 mg/dl					

Blood film on 11/18 showed the cells to be normocytic, normochromic histiocytes 3+, microspherocytes 2+, platelets markedly decreased. Sternal marrow: hypercellular 3+. Megakaryocytes: adequate to increased. Erythropoiesis: normoblastic. Urinalysis: blood, 2+; bacteria, 2+; albumin, 3+, WBC, clumps; RBC, 2-3 HPF. Chest x-ray: pulmonary infiltrates; changes consistent with pulmonary edema. ECG: within normal limits; sinus tachycardia. EEG: diffuse encephalopathy.

multiple ecchymoses over both extremities, bleeding gums, and a small left retinal hemorrhage in a stuporous patient responding only to painful stimuli, but without focal neurologic deficit. X-ray revealed pulmonary congestion with rhonchi and rales over both lung fields on auscultation. Laboratory, ECG, x-ray and EEG reports are shown in table.

Digitalis and diuretics had been started earlier, to which was added acetylsalicylic acid 900 mg; methylprednisolone 300 mg; dipyrimadole 100 mg; each 6 hourly via nasogastric tube.

Anesthetic Management.—The patient was premedicated with 0.4 mg of atropine IV and then preoxygenated for 5 minutes. Anesthesia was induced with 10 mg of pancuronium bromide followed by 150 mg of thiopental; cricoid pressure was exerted until endotracheal intubation had been achieved. Maintenance was with N_2O-O_2 (3:3) and a supplement of 2 ml of Innovar®. Frothy material was present on endotracheal suctioning and central venous pressure (CVP) was 22 cm H_2O. In view of this, chlorpromazine was given to a total of 22.5 mg. By the end of the 2-hour operation, the blood loss was partly replaced with packed cells, the CVP had fallen to 11 cm H_2O, and 130 ml of urine had been produced. Postoperatively, she was ventilated at an F_{IO_2} of 0.5 to maintain a P_{aO_2} >100 torr.

The following morning she was not fully conscious; her wound continued to ooze, she had bloody nasogastric aspirate, and had received 4 units of packed cells. As she then started to lose blood vaginally, labor was induced by membrane rupture and pitocin infusion. Shortly thereafter, an 800-gm fetus was born, surviving for 7 hours. The placenta was normal, and neither blood studies nor autopsy revealed any fetal abnormalities.

By the 2nd postoperative day, she had improved sufficiently to permit spontaneous ventilation and subsequent extubation. She now responded to both tactile and verbal stimuli. On the 3rd postoperative day, improvement continued, bleeding started to abate, and the platelet count rose daily to 120,000/cu m on the 7th day. By the 10th day, she was transferred to the original hospital.

Histopathology.—The spleen (315 gm) was considerably enlarged. The parenchyma was uniformly violaceous, with few discernible follicles. The splenic artery and vein were patent. Numerous follicular and penicillar arteries were found to be occluded by microthrombi. The red pulp had a few foci of hematopoiesis with megakaryocytes. These morphologic changes were interpreted to represent intravascular coagulation, suggestive of thrombotic thrombocytopenic purpura.

DISCUSSION

The symptom pentad of TTP[3] includes: (1) thrombocytopenic purpura, (2) hemolytic anemia, (3) changing mental status, (4) fever, and (5) renal involvement. A clinical diagnosis of TTP could not be positively differentiated from DIC from some other cause in this patient. Some features, common to both diseases, such as intravascular coagulation and microthrombi, causing multiple organ failure, are worthy of anesthetic consideration.

Preoperatively, measures to bring such patients to optimum condition include:

(1) Control of cardiac failure by digitalis and diuretics. In addition, peripheral vasodilation will benefit the patient by its effect as internal phlebotomy, possible improvement of renal perfusion, and by reducing the tendency to "sludging" and further thrombosis.

(2) Maintenance of adequate tissue oxygenation, which may be difficult in the presence of pulmonary insufficiency, low cardiac output, and low hemoglobin, some of which is free in the plasma and not contributory to O_2 transport. The pulmonary insufficiency from the multiple infarcts and incipient pulmonary edema may be helped by CPPB or CPAP, which may produce a rise in arterial O_2 tension. While this must be balanced against hypotension produced by the reduction in venous return, it may possibly improve both oxygenation and cardiac output.[9,10]

(3) Monitoring should include blood pressure, CVP, and possibly left atrial or pulmonary wedge pressure via a 4-channel Swan-Ganz catheter for combined right atrial and pulmonary wedge pressure monitors, as both sides of the heart may be in failure because of microemboli; in addition, it provides access to left atrial (arterial) blood for blood-gas analysis and can be used for all blood sampling, avoiding the risks of hematoma following venipuncture and preserving veins for the inevitable transfusions. Arterial punctures or cannulation in the presence of thrombotic processes may be open to criticism if the patient is not adequately heparinized.

(4) Blood volume should be restored cautiously, with full monitoring of blood pressure, CVP, urine output, and left atrial pressure. It must be borne in mind that platelets may accelerate the disease process, especially in the absence of heparinization; fresh blood may be contraindicated, but fresh frozen plasma is platelet poor and frozen red cells are platelet free.

(5) Fluid and electrolyte imbalance may be aggravated by renal failure and by the administration of steroids. Renal involvement occurs early, both as a result of the disease process and precipitation of the free hemoglobin in the plasma and in the renal tubules, the severity varying from microscopic hematuria to anuria. Alkalinization, diuretics, vasodilators (perhaps a specific renal vasodilator such as dopamine) should be considered. Dextran 70 may have a special place, as it acts by coating both vessels and platelets to prevent platelet aggregation, which is the initial process in thrombus formation.

(6) Serum K^+ values may be high from both hemolysis and renal involvement, and the use of a depolarizing agent such as succinylcholine may precipitate ventricular arrhythmias and even cardiac arrest.[11] However, as most such cases are seen on an emergency basis, rapid relaxation and intubation are necessary to minimize the risk of aspiration of gastric contents and should be intense enough to permit atraumatic insertion of the endotracheal tube, essential in a patient with hemorrhagic diathesis. It has been shown that 0.15 mg/kg of pancuronium achieves good intubating conditions within 30 seconds,[12] and this, combined with cricoid pressure (Sellick's maneuver), was the technic used here.

(7) Fibrinolysis is either primary or secondary to DIC and extremely difficult to differentiate. Hence, administration of epsilon-aminocaproic acid (Amicar®), the drug of choice for primary fibrinolysis, is not recommended unless it is given IV after a dose of 0.5 mg/kg of IV heparin. If Amicar is given to patients thought to have primary fibrinolysis, who had in fact DIC, disastrous thromboembolic complications can occur.[13] In most cases, DIC can be successfully treated by restoring blood volume, preferably with fresh blood, and by maintaining tissue perfusion.

Most pregnancies in such cases terminate by stillbirth or abortion, but live births (3/10) have occurred, with the neonate showing no abnormalities.[14] It should be mentioned that septic abortion with renal failure mimics TTP clinically, and evacuation of the uterus should be considered if there is no improvement in the clinical condition of the patient.

EPILOGUE

This patient became pregnant again and delivered a normal 3030 gm male child on 1/30/75 without problems. Her hematologic profile was normal.

REFERENCES

1. Moschcowitz E: An acute febrile, pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries. An undescribed disease. Arch Intern Med 36:89-93, 1925

2. Cuttner J: Splenectomy, steroids and dextran 70 in thrombotic thrombocytopenic purpura. JAMA 227:397-402, 1974

3. Amorosi EL, Ultmann JE: Thrombotic thrombocytopenic purpura: report of 16 cases and review of the literature. Medicine 45:139-159, 1966

4. Allanby KD, Huntsman RG, Sacker LS: Thrombotic microangiopathy. Recovery of a case after heparin and magnesium therapy. Lancet 1:237-239, 1966

5. Lerner RG, Rapaport SI, Meltzer J: Thrombotic thrombocytopenic purpura. Serial clotting studies, relation to generalized Shwartzman reaction, and remission after adrenal steroid and dextran therapy. Ann Intern Med 66:1180-1190, 1967

6. Miller RD: Transfusion therapy and associated problems. Reg Refresh Courses Anesth 1:101-113, 1973

7. Friedman NJ, Hoag MS, Robinson AJ, et al: Hemorrhagic syndrome following transurethral prostatic resection for benign adenoma. Arch Intern Med 124:341-399, 1969

8. Miller RD, Robbins TO, Tong MJ: Coagulation defects associated with massive blood transfusions. Ann Surg 174:794-801, 1971

9. Colgan FJ, Nichols FA, DeWeese JA: Positive end-expiratory pressure, oxygen transport, and the low-output state. Anesth & Analg 53:538-543, 1974

10. Trichet B, Falke K, Yogut A, et al: The effect of pre-existing pulmonary vascular disease on the response to mechanical ventilation with PEEP. Anesthesiology 42-56-67, 1975

11. Koide M, Waud BE: Serum potassium concentrations after succinylcholine in patients with renal failure. Anesthesiology 36:142-145, 1972

12. Dalal FY, Bennett EJ: The safety of pancuronium in renal failure. Madrid, Spain, Proceedings of the Fourth European Congress of Anesthesiologists, September 5-12, 1974

13. Robboy S. Colman R, Minna J: Fibrinolysis vs disseminated intravascular coagulation. N Engl J Med 281:222, 1969

14. Yudis M, Reid J, Burd R, et al: Septic abortion masquerading as thrombotic thrombocytopenic purpura. Am J Obstet Gynecol 3:350-352, 1971

PREGNANCY TEST Each year more than 12 million women of child bearing age are admitted to US hospitals. The possibility of early pregnancy should be considered in these patients prior to medical or surgical care. However, a survey of 224 hospitals with 200 beds or more revealed routine pregnancy tests were performed by only 3 per cent of private and municipal hospitals, 20 per cent of hospitals for the mentally retarded and by no psychiatric hospitals. A pregnancy test is simple and inexpensive and easily performed on the urine samples collected on admission. Such a test should be performed on all women of child bearing age especially if they are scheduled for surgery or radiographic investigation. *(Laubach GE Wilchins SA: Routine pregnancy test on admission to hospital. Am J Ob Gyn 123:691-694, 1975)*

"Pentazepam" (Pentazocine + Diazepam) Supplementing Local Analgesia for Laparoscopic Sterilization

J. ANTONIO ALDRETE, MD, MS*
SHIRLEY T. TAN, MD†
DONALD J. CARROW, MD‡
MARY K. WATTS, CRNA§
Louisville, Kentucky‖

Salpingectomy by laparoscopy in 200 healthy outpatients employed local analgesia and "pentazepam" (pentazocine 90 mg and diazepam 30 mg in 250 ml of 5% D/W) as anesthesia. Patients received no premedication, ventilated spontaneously, without tracheal intubation, but were given nasal O_2 at 3 L/min throughout the procedure. N_2O was used for abdominal insufflation, and the abdominal pressure and Trendelenburg position were restricted to less than 20 cm H_2O pressure and 30°, respectively. Changes in arterial blood gases measured in 12 patients were unremarkable. Prolonged recovery, unsatisfactory surgical conditions, tachycardia, nausea and vomiting were infrequent.

SALPINGECTOMY through a laparoscope has become a common sterilization procedure. Surgically, this appears a relatively simple procedure, and large series have been reported[1,2] with few complications.

The high demand for this endoscopic procedure and its apparent simplicity have encouraged its consideration for ambulatory patients. However, from the anesthetic point of view, it is by no means a minor procedure. The insufflation of a highly diffusible gas, commonly CO_2, within the abdominal cavity, to separate the abdominal wall from its contents, brings about hypercarbia[3,4] and its subsequent hemodynamic and metabolic effects. Even if CO_2 is substituted for N_2O, the elevated intraabdominal pressures required to attain the desired operative conditions exert undue pressure on the diaphragm; in addition, if the frequently used Trendelenburg position is extreme, these factors combined would produce marked impairment of ventilation.[5]

To assure proper respiratory function during this time and prevent the possible dangers of regurgitation and aspiration of gastric contents, endotracheal intubation has been recommended almost routinely. This technic, along with the use of muscle relaxant drugs and other longer-lasting anesthetic agents, appears to be overtreatment for patients who in a few hours will be returning home.

The foregoing considerations, and the desire for an alternative that would offer anesthetic safety with proper operative conditions, led us to evaluate pentazepam, a combination of the analgesic pentazocine with

*Currently Professor and Chairman, Department of Anesthesiology, University of Colorado Medical School, Denver, Colorado 80220.

†Assistant Professor, Department of Anesthesiology, University of Colorado School of Medicine, Denver, Colorado 80220.

‡Assistant Professor, Department of Anesthesiology, University of Louisville School of Medicine, Louisville, Kentucky 40202.

§Nurse Anesthetist, Louisville General Hospital.

‖Department of Anesthesiology, University of Louisville School of Medicine, Louisville, Kentucky 40202.

Paper received: 5/22/75
Accepted for publication: 6/27/75

the tranquilizer-amnesic diazepam, which, jointly used with local analgesia, would provide the expected conditions.

METHODS

This study includes 200 women between the ages of 22 and 43 years, all within ASA physical status I, electively scheduled for outpatient bilateral laparoscopic salpingectomy. None had a history of pelvic inflammatory disease or of lower abdominal surgery. A physical examination, chest x-ray, urinalysis, hemoglobin, and blood count were performed the day before the procedure. Patients were instructed not to drink or eat anything after midnight and were given a complete explanation of the procedure.

Admission to the hospital was scheduled for 0700 hr, and soon thereafter patients were taken to the operating room. An IV indwelling catheter was inserted, with lactated Ringer's solution. Monitoring was by precordial stethoscope, blood pressure cuff, and bipolar ECG. No premedication was given.

After obtaining initial values of heart rate, arterial blood pressure, and respiration, the pentazepam solution, consisting of pentazocine and diazepam (90:30 mg) in 250 ml of 5% D/W, was initiated as previously described[6] at a rate of 30 ml/min. This rate was maintained until patients closed their eyes spontaneously and appeared to be in deep sleep, though they were able to follow commands (take a deep breath, open your eyes, etc) or responded to severe painful stimulation. The remaining solution was then infused at a rate of 4 ml/min, until the moment of cauterization of the second uterine tube, at which time it was stopped.

Even before patients closed their eyes completely, but when signs of somnolence were seen, they were placed in a modified lithotomy position and their abdomen and vagina were scrubbed with soap and antiseptic solutions. A cervical suction cannula was introduced and the bladder emptied by catheterization. After draping, 6 ml of 1% lidocaine solution was injected in the lower rim of the umbilicus and underlying tissues.

Operation was usually started before 0800 hr. While lifting up the anterior abdominal wall, the surgeons inserted a Verres cannula into the abdominal cavity, and N_2O was initially insufflated until the abdomen appeared moderately distended. A 10-mm trochar was then introduced through which a Wolf laparoscope was passed after enough N_2O was insufflated to obtain adequate visualization but never to exceed 20 cm H_2O pressure within the abdomen, the total amount of N_2O insufflated ranging from 6 to 9.5 L. At this time, the patient was placed in a 20° Trendelenburg position. Oxygen (3 L/min) was administered by nasal prongs and vital signs were monitored throughout.

At the completion of the surgical procedure, patients were taken to the recovery room, evaluated by means of the Postanesthetic Recovery (PAR) Score,[7] and kept under close supervision until their discharge to the gynecologic outpatient recovery unit, remaining there until 1400 hr. Initially, to evaluate the effects of this technic on respiratory function, arterial blood gases and pH were measured in 12 patients.

In some cases when unsatisfactory conditions were noted, the anesthesia was supplemented by intermittent 25-mg doses of sodium thiopental or 50% N_2O-O_2 inhalation by mask. In the event of surgical complications requiring laparotomy, endotracheal intubation was performed with the aid of muscle relaxants and conventional anesthetic technics followed. All anesthetics were administered by either anesthesiology residents or nurse anesthetists under the supervision of staff anesthesiologists.

RESULTS

The mean age of the patients was 27.8 years and average weight was 56.4 kg. The average anesthetic and operative time was 39.4 and 24.8 minutes, respectively.

Satisfactory operative conditions with pentazepam and lidocaine alone were obtained in 176 patients. In these, an average of 142 ml of pentazepam solution was required to obtain the neuroleptic state similar to that observed with the administration of Innovar®. In 24 patients, the entire 250 ml was given.

Sodium thiopental had to be administered in 10 cases, and more diazepam (5 to 10 mg IV) in 34 others. In addition, N_2O was used as an adjuvant in 4 patients.

Untoward Reactions.—Tachycardia exceeding 25% of the preanesthetic heart rate was noted in 12 patients (5%), premature ventricular contractions and hypotension were seen only once each (0.5%) in sepa-

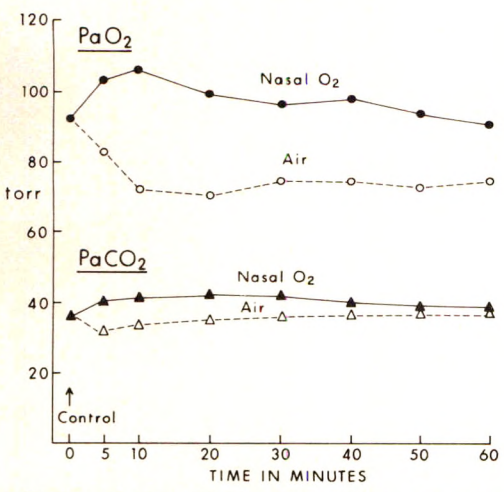


FIGURE. Average blood gas analysis in two groups of six patients each, breathing air and nasal oxygen.

rate patients. The former was treated with 60 mg of lidocaine HCl by IV bolus and the latter with fluid administration. Prolonged recovery (exceeding 120 minutes) was observed in 8 cases (4%). Nausea and vomiting occurred in 10 patients (5%).

The average recovery room stay was 57 minutes, with mean PAR scores at arrival of 8.08, all patients achieving scores of 10 before being discharged to the ward.

Because of surgical complications, 6 patients were hospitalized, 4 having undergone laparotomies either at the time or within 24 hours of the laparoscopy. One patient suffered a small skin burn from the cautery.

Blood-Gas Analysis (figure).—In the first group of 6 patients allowed to breathe room air, a decline of Pao_2 was noted during the first 30 minutes of the procedure. This, however, was prevented in the subsequent 6 patients, in whom nasal O_2 was administered at the rate of 3 L/min. Changes in CO_2, pH, and bicarbonate were not significant.

The mean postanesthetic scores at recovery-room arrival and progress to discharge are shown in the table.

DISCUSSION

In view of current trends, it is likely that bilateral salpingectomy will be increasingly frequent for permanent sterilization. Use of the laparoscope has greatly facilitated this operation, with minimal tissue injury.

It remains a challenge to the anesthesiologist to develop a technic that will avoid patient discomfort and pain and permit satisfactory surgical conditions without sacrificing patient safety. For socioeconomic reasons, an outpatient basis is also a desirable factor. (In other words, let us not give a 6-hour anesthetic for a 30-minute operation.) In this spirit, the technic described, which preserves adequate respiratory exchange without the need of endotracheal intubation, was developed. This maneuver, though safe in most instances, carries a certain morbidity and requires muscle relaxation and/or a deep level of anesthesia.

We previously reported the application of pentazepam as a supplement to local analgesia for laryngoscopy,[8] bronchoscopy, ventriculojugular shunt revision,[6] and inguinal herniorrhaphy[9] in elderly patients. Also, semiawake poor-risk patients with full stomach were intubated endotracheally with satisfactory results.[6] Other authors have used

TABLE
Postanesthetic Recovery Scores in Patients Undergoing Laparoscopic Tubal Ligations

Score	Arrival	15 minutes	30 minutes	60 minutes
Number of patients	200	200	184 (92)	160 (80)
10	58 (29)	105 (52.5)	151 (82)	143 (89.4)
9	63 (31.5)	54 (27)	12 (6.5)	8 (5)
8	39 (19.5)	19 (9.5)	9 (5)	1 (0.6)
7	22 (11)	12 (6)	4 (2.2)	8 (5)
6	10 (5)	2 (1)	8 (4.3)	0
5	8 (4)	8 (4)	0	0

Figures in parentheses indicate percentage.

this combination for minor gynecologic procedures,[10] as a supplement to regional anesthesia,[11] and for cardiovascular surgical procedures.[12]

Throughout these observations, the following pharmacologic advantages appear evident: minimal hemodynamic alterations, with no change of heart rate; moderate analgesia; excellent amnesia; and adequate sedation. A certain degree of respiratory depression can occur in cases of excessive dosage; however, this is usually compensated by surgical stimulation or can be easily antagonized by the administration of the analeptic, doxapram HCl. Overdosage can also result in prolonged recovery and occasionally in nausea and vomiting.

In the event of inadequate analgesia and sedation, small doses of diazepam, thiopental, or inhalation of N_2O were enough to achieve quasi-ideal conditions. This fact warrants the need for an experienced anesthesiologist at "the head of the table," and we would not advise its use without vigilant attention to the patient.

The high percentage of patients arriving at the recovery room with PAR scores of 10 indicates the alertness of these patients at this moment, most of whom could have been sent directly to the ward (table).

The amnesic properties of diazepam are invaluable, since the majority of patients barely remembered the initiation of the venoclysis and had no recall of what went on during the procedure, though they were able to communicate with the anesthesiologist. Though sedation was satisfactory, pharyngeal and laryngeal reflexes were maintained active, with patients either swallowing or coughing whenever salivary secretions were present.

The fact that premedication was not necessary saved time, expense, and discomfort to the patient, permitting faster recovery. As before,[6] we feel that if specific premedication is required for a technic to be effective, that technic is not completely dependable.

The apparent effectiveness of pentazepam for this operation may be due to the close adherence to the following guidelines agreed to by the surgeon-anesthesiologist team:

1. Consider only healthy women, within ASA class I.
2. Avoid CO_2 for insufflation.
3. Limit intraabdominal pressure to 20 cm H_2O.
4. Limit the operating time to 40 minutes.
5. Limit the Trendelenburg position, when needed, to 30° incline.

If any of these standards cannot be followed, we recommend other conventional anesthetic technics.[3-5]

By following these guidelines some other complications such as pneumothorax,[13] narrowing of pulse pressure due to large-vessel compression,[5] and occasional sore throat[14] will also be prevented. Hypercarbia and hypoxemia, noted in other studies[3,4,15,16] also can be avoided.

The need for O_2 supplementation in these procedures was also substantiated in a study by Baratz and Karis,[15] who noticed that even intubated patients undergoing laparoscopy with controlled ventilation needed to breathe at least 50% O_2 to maintain adequate Pao_2.

REFERENCES

1. Black WP: Sterilization by laparoscopic tubal electrocoagulation: an assessment. Amer J Obstet Gynec 3:979-983, 1971

2. Wheeless CR Jr: The status of outpatient tubal sterilization by laparoscopy: improved techniques and review of 1000 cases. Obstet Gynec 39: 635-636, 1972

3. Hodgson C, McClelland RM, Newton JR: Some effects of peritoneal insufflation of carbon dioxide at laparoscopy. Anaesthesia 25:382-390, 1970

4. Seed RF, Shakespeare TF, Muldoon MJ: Carbon dioxide homeostasis during anaesthesia for laparoscopy. Anaesthesia 25:223-231, 1970

5. Alexander GD, Noe FE, Brown EM: Anesthesia for pelvic laparoscopy. Anesth & Analg 48:14-18, 1969

6. Aldrete JA, Clapp HW, Fishman J, et al: "Pentazepam:" a supplementary agent. Anesth & Analg 50:498-504, 1971

7. Aldrete JA, Kroulik D: A postanesthetic recovery score. Anesth & Analg 49:924-934, 1970

8. Aldrete JA: Respiratory changes during laryngoscopy: influence of the anesthetic technique. ORL Digest 33:29-35, 1971

9. Guillen J, Aldrete JA: Anesthetic factors influencing morbidity and mortality of elderly patients undergoing inguinal herniorrhapy. Amer J Surg 120:760-763, 1970

10. Schoenfeld A, Goldman JA, Levy E: Pentazocine and diazepam analgesia for minor gynecological operations. Brit J Anaesth 46:385-386, 1974

11. Jourde J, Peri G, Menes H, et al: The value of associating diazepam and pentazocine in an

anesthetic contest in maxillo-facial surgery. Ann Anes France 13:173-177, 1972

12. Hatano S, Keane D, Wade MA, et al: Diazepam-pentazocine anaesthesia for cardiovascular surgery. Canad Anaesth Soc J 21:586-599, 1974

13. Doctor NH, Hussain Z: Bilateral pneumothorax associated with laparoscopy. Anaesthesia 28: 75-81, 1973

14. Pent D, Loffer FD: Laparoscopy at the surgicenter. J Reprod Med 10:239-242, 1973

15. Baratz RA, Karis JH: Blood gas studies during laparoscopy under general anesthesia. Anesthesiology 30:463-464, 1969

16. Drury WL, LaVallee DA, Vacanti CJ: Effects of laparoscopic tubal ligation on arterial blood gases. Anesth & Analg 50:349-351, 1971

POSTOPERATIVE PAIN The efficacy of transcutaneous electrical stimulation in alleviating acute pain following abdominal or thoracic operations was evaluated in a prospective study. Forty-seven of 61 patients (77 per cent) experienced pain relief with transcutaneous electrical stimulation. Of these, 15 patients experienced complete pain relief and required no analgesic medication. Most were able to cough and breath deeply without significant pain during stimulation. Thirty-two of 39 patients (83 per cent) experienced no pain relief with mock stimulation. Transcutaneous electrical stimulation may serve as a useful adjunct to the postoperative alleviation of pain without the depressant or addictive hazards present with narcotics. *(VanderArk GD, McGrath KA: Transcutaneous electrical stimulation in treatment of postoperative pain. Am J Surg 130:338-340, 1975)*

MECONIUM ASPIRATION A retrospective study of 125 infants born through meconium stained amniotic fluid was performed. Forty-three newborns developed respiratory distress and 8 died. Of 97 infants receiving tracheal suction in the delivery room only 27 developed respiratory distress and 1 died. In contrast, 16 of 28 patients not receiving immediate tracheal suction developed respiratory distress and 7 died. Steroids and antibiotics did not alter the outcome. Immediate tracheal suction and removal of meconium are important in the management of infants born through meconium stained amniotic fluid. *(Ting P, Brady JP: Tracheal suction in meconium aspiration. Am J Ob Gyn 122:767-771, 1975)*

Survival Following Massive Pulmonary Hemorrhage Complicating Pulmonary Embolectomy: A Case Report

STUART B. WOLLMAN, MD*
LAWRENCE G. KUSHINS, MD†
New Hyde Park, New York‡

Continued employment of extracorporeal circulation provides for adequate oxygenation despite massive pulmonary hemorrhage. However, this modality requires continuing heparinization, which seems to preclude control of the hemorrhage. The longer bleeding persists, the more the pulmonary damage. Further, the problems of massive volume replacement will be added to this catastrophe. The authors believe that rapid discontinuance of extracorporeal bypass, reversal of heparinization with protamine, aggressive pulmonary suctioning, and alternate ventilation with 100% O_2 were responsible for their good result. Arterial hypoxemia was avoided despite pulmonary suction yielding 1500 ml in 17 minutes.

MASSIVE pulmonary hemorrhage has been reported to complicate pulmonary embolectomy when pulmonary circulation is reestablished. Of 8 reported cases of acute pulmonary hemorrhage,[1-3] only 1 patient survived. We are presenting the case of a second survivor, with a discussion of this entity and of therapy utilized in successful treatment. Although others[1,3] have minimized the role of reversal of heparinization with protamine, the dramatic response of our patient to this measure should be brought to the attention of cardiovascular surgical teams.

PATIENT HISTORY

A 37-year-old man suffered a ruptured spleen, fractured pelvis, lacerated left kidney, and multiple fractures of his left lower rib cage in an automobile accident on November 12, 1974, undergoing a splenectomy and repair of the lacerated kidney on that date. Postoperatively, his pulmonary status was a major problem, with extensive consolidation of the left lung field on x-ray. Pao_2 on room air was 34 torr on the 2nd postoperative day. He was treated with 100% O_2 by face mask, bringing his Pao_2 to 54 torr. He rapidly improved in the next 24 hours, so that FIO_2 was gradually reduced to 0.45, with Pao_2 in the range of 60 to 70 torr. On the 8th postoperative day, his Pao_2 on room air was 66 torr.

The possibility of fat embolism was treated with 1 gm of IV methylprednisolone sodium succinate NF on 2 successive days, although no diagnosis was proven. Heparin (5000 units) had been given subcutaneously twice a day as prophylaxis for the prolonged bed rest contemplated in the treatment of his pelvic fractures, starting on November 15 and continuing for 2 weeks. On November 28, 1974, following ambulation, the patient developed diaphoresis, tachycardia, hypotension, and fever (39.4 C). He complained of "tight" precordial chest pain. The ECG exhibited inverted T waves over the precordium. A lung scan

*Staff Anesthesiologist.

†Resident in Anesthesiology.

‡Department of Anesthesiology, Long Island Jewish Hillside Medical Center, New Hyde Park, New York 11040.

Paper received: 5/19/75
Accepted for publication: 8/7/75

showed a right upper lobe defect. Pulmonary angiography demonstrated a saddle embolus in the main pulmonary artery as well as right upper lobe and left middle lobe involvement. After a total of 26 hours without improvement, he was taken to the operating room for pulmonary embolectomy and clipping of the inferior vena cava.

On arrival in the operating room, vital signs were temperatures 39.4 C, pulse 132 bpm, respiration 28/min, BP 90/60 torr. CVP was 20 cm H_2O. Because of his precarious cardiovascular status, ketamine was used for induction and pancuronium for endotracheal intubation. Blood gases, with the patient breathing 100% O_2 via a semiclosed anesthesia system, were pH 7.40, $Paco_2$ 33 torr, and Pao_2 129 torr. Anesthesia was maintained with 2% fluroxene in O_2. After heparinization with 300 units/kg, extracorporeal bypass via a Bentley membrane oxygenator and Sarnes pump was instituted. The ascending aorta was cannulated and the venae cavae were cannulated via the right atrium. Moderate hypothermia to 33 C was induced. Two percent fluroxene, 2% CO_2, and 96% O_2 were administered via pump.

Upon opening the pulmonary artery, multiple clots were found in the main, right, and left pulmonary arteries and their lobar branches. Both lungs were severely blanched. Pulmonary embolectomy was performed with forceps, Foley catheter, pulmonary massage, and suctioning. Upon closure of the pulmonary artery and institution of partial bypass, both lungs were noted to be rigid and not expanding with ventilation. Almost immediately, massive amounts of bloody fluid were noted in the endotracheal tube.

Rapid IV administration of 0.25 mg of digoxin, 40 mg of furosemide, and 1 gm of hydrocortisone produced no reduction in hemorrhage. Upon noting 1500 ml of suctioned blood in a period of 17 minutes, extracorporeal bypass was abandoned and 4 mg/kg of protamine was administered. Hemorrhage stopped almost immediately. Sixty minutes elapsed between heparinization and the start of protamine administration. Blood gases drawn during this episode and the subsequent half hour showed Pao_2 ranging from 160 to 285 torr. Ventilation was with 100% O_2 during this period except during endotracheal suction. Mild acidosis was treated with 89.2 mEq of $NaHCO_3$. Rewarming had commenced with closure of the pulmonary artery, and the patient's rectal temperature was 36 C when bypass was concluded.

Ligation of the inferior vena cava and operative closure were uneventful. Postoperative chest x-rays initially revealed "a left lower lobe infiltrate, a small left pleural effusion, atelectasis of the right base, and an infiltrate of the right cardiophrenic angle." Postoperative arterial blood gases showed steadily decreasing alveolar:arterial differences in O_2 levels. Follow-up chest x-ray showed steady improvement, and no further pulmonary embolization or hemorrhage was evidenced. The patient's most persistent problem was phlebitis of the left leg, which was treated with heparin on the 5th postoperative day and later changed to sodium warfarin. He was discharged on the 23rd postoperative day.

DISCUSSION

The etiology of massive pulmonary hemorrhage following pulmonary embolectomy is unclear. Common to all cases is a period of hypotension and pulmonary hypoperfusion with damage to pulmonary capillaries, leading to hemorrhagic pulmonary infarction when blood flow is reestablished following embolectomy. While it is not clear from the literature, reports of the use of Carlens endobronchial tubes to isolate unilateral pulmonary bleeding[1] suggest this complication to be the result of local injury due to the embolus, although our patient showed no evidence of unilateral hemorrhage. This problem has occurred with both short[1] and long[2,4] periods between embolization and embolectomy, with a high incidence of this problem expected in the "chronic" embolectomy patient.[4]

Delayed pulmonary hemorrhage has been reported following embolectomy for chronic recurrent emboli.[4] However, this occurred as a late complication, hours after operation, and was of a lesser magnitude with a favorable outcome. The use of cardiopulmonary bypass and heparinization is not standard for the removal of thrombi in "chronic" embolectomy, and when pulmonary hemorrhage has been reported in the absence of bypass and heparin, it has been less severe and survival is more common. Heparinization appears to greatly increase the severity of postembolic pulmonary hemorrhage, although this entity has been reported in the absence of extracorporeal bypass in 1 case.[3]

Makey's group[1] postulated corticosteroid-related abnormalities, since their 2 cases

and that published by Castleman[2] were either on chronic steroid therapy or showed adrenal pathology at necropsy. However, 5 subsequent cases, including the single previous survivor described by Couves and associates,[3] yielded no hint of steroid abnormalities.

Treatment of massive pulmonary hemorrhage following pulmonary embolectomy presents a dilemma and a gamble to the operative team.

We realize that our actions were a gamble that oxygenation could be maintained. However, it was also clear that pulmonary hemorrhage at the rate described, with no sign of abatement, would prove rapidly fatal. Our later search of the literature confirmed our instincts. Of 8 patients with acute hemorrhage immediately following reinstitution of pulmonary circulation, 7 died. Only our patient and Couves' sole survivor were treated with protamine after discontinuing bypass. Of the 7 fatalities, only 1 patient was taken off bypass and given protamine. In that case, heparinization was apparently reversed by slow titration, and then only after a prolonged period of pulmonary hemorrhage.

On the basis of the outcome of previous cases reported, we recommend the use of protamine as rapidly as extracorporeal circulatory bypass can be abandoned. Since this complication occurs when the pulmonary artery is closed, such action does not compromise the operative procedure. The temptation to remain on bypass should be resisted. Such measures as digitalization, steroids, and diuretics may be of value but do not appear to have had a crucial influence on the outcome.

Although this is a strong position to take on the basis of only 2 survivors out of 9 reported patients, the treatment we recommend is the only one that has, to date, proved successful. Only further experience will show if this course of action is consistently effective.

REFERENCES

1. Makey AR, Bliss PP, Ikram H, et al: Fatal intra-alveolar pulmonary bleeding complicating pulmonary embolectomy. Thorax 26:466-471, 1971

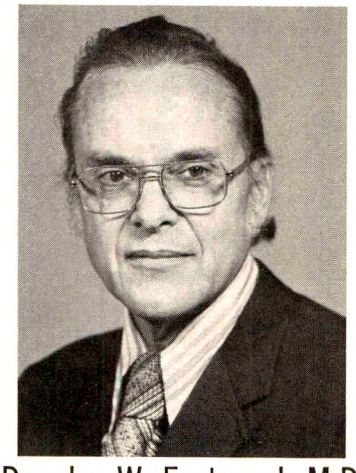
2. Castleman B: Case records of the Massachusetts General Hospital. N Engl J Med 271:40-50, 1964

3. Couves CM, Nakat SS, Sterns LP, et al: Hemorrhagic lung syndrome. Ann Thorac Surg 15: 187-195, 1973

4. Moser EM, Braunwald NA: Successful surgical intervention in severe chronic thromboembolic pulmonary hypertension. Chest 64:29-35, 1973

MYOCARDIAL PROTECTION Patients undergoing coronary revascularization are at an increased risk if preinfarction angina and/or ventricular dysfunction (ejection fraction <0.4) are present (high risk patients). Postoperative mortality, infarction and need for inotropic support are greater in these patients as compared with patients without continuous angina or ventricular dysfunction (low risk patients). To reduce the hazard of ischemic injury the following principles of management are recommended: 1) avoid extreme blood pressure changes, 2) monitor left ventricular filling pressure, 3) vent the left ventricle, 4) perform all anastomoses during cardiopulmonary bypass, 5) maintain perfusion pressure >75 Torr, 6) avoid extreme hemodilution, 7) avoid ventricular fibrillation, 8) use intermittent ischemia arrest, 9) repay O_2 debts by prolongation of cardiopulmonary bypass if neccessary. Employing these principles, the need for inotropic support, postoperative infarction and mortality were similar in high and low risk patients. *(Olinger GN, Po J, Maloney JV et al: Coronary revascularization in high versus low risk patients. The role of myocardial protection. Ann Surg 182:293-300, 1975)*

We Salute . . .



Douglas W. Eastwood, M.D.

DOUGLAS W. EASTWOOD can be described in many terms—intelligent, innovative, pragmatic, indefatigable. Those who have worked with him know him also as a superb clinician and teacher.

Doug Eastwood was born the son of a minister in Ellsworth, Wisconsin, in 1918. Moving to Iowa, Doug completed his premedical education at Coe College and subsequently attended and graduated from the University of Iowa College of Medicine in 1943. After a year's residency in Internal Medicine at Detroit Receiving Hospital, he entered the United States Army and served in the European theater. On his return, he entered a residency in anesthesia at the University of Iowa under the direction of Dr. Stuart Cullen. He continued his medical education following completion of his residency, receiving a Master of Science in Pharmacology from the Graduate College of Iowa, after which he served as Instructor and Associate in the Department of Anesthesia.

Doug's clinical and teaching objectives soon crystallized, and in 1950 he accepted a position as Chief of the Division of Anesthesiology at Washington University, St. Louis. Four years later, Doug returned to the University of Iowa as Associate Professor, and in 1955 was appointed Chairman of the Department of Anesthesiology at the University of Virginia Medical Center, Charlottesville.

During the next 15 years in Charlottesville, Doug labored to develop a fledgling department into one that enjoys a national reputation as a training center. Many of his former residents continued in academic positions, to further Doug's clinical and research concepts. His greatest strength has always been the clinical classroom—the operating theater. His technical skill and superb judgment in a clinical setting are widely recognized and readily appreciated by his colleagues. As an innovator, Doug worked on the early development of ventilators and pulse monitors. The first use

of Computer-Assisted Instruction at the University of Virginia Medical Center was implemented by Doug Eastwood and supported by the Department of Anesthesiology.

His constant concern for improvement of teaching technics stimulated Doug to relinquish his Chairmanship to take a year's leave of absence to seek further training in learning methodology. Toward this goal, he was appointed to the Lister Hill National Center for Biomedical Communication of the National Library of Medicine. During that period, he investigated the role of the academic community in the application of educational technology.

In 1972, he joined the faculty at Case Western Reserve Medical Center as Professor of Anesthesiology, with a joint appointment in the Division of Research in Medical Education. In these, his current positions, he is devoting most of his time to graduate medical education while yet maintaining close contact with clinical teaching in the operating room.

Dr. Eastwood is a member of professional and scholarly societies which include Sigma Xi, the American Society of Anesthesiologists, the International Anesthesia Research Society, and the Association of University Anesthetists. He is a diplomate of the American Board of Anesthesiology and a Fellow of the American College of Anesthesiologists. His professional activities include many years of service to the ASA and particularly to the College. He has served as Chairman and Vice-Chairman of the ASA Annual Meetings, and as Chairman of the College Education Resources and Written Examination Committees. He has recently been nominated as President-Elect of the College.

Since 1968, Doug has been an Associate Editor of *Survey of Anesthesiology*. His concern for education has carried him as a consultant to Tanzania for both the World Bank and the United Nations, to evaluate and make recommendations for the expansion of medical education in that country. His numerous scientific publications have been widely recognized, particularly his scholarly work on nitrous oxide.

Doug and his lovely wife, Ruth, have four children and reside in Cleveland Heights, Ohio.

It is with pleasure that we salute our colleague for his many talents and achievements in medicine and anesthesia.

PHENYLEPHRINE-NITROGLYCERIN The effects of combined intravenous nitroglycerin and phenylephrine therapy on the sum of ST segment elevation (ΣST) was determined in 10 patients following acute myocardial infarction. Nitroglycerin reduced mean arterial pressure 22 Torr and left ventricular filling pressure 8 Torr. ΣST decreased 17 mm at the time of maximum hemodynamic effect. Addition of phenylephrine to return the blood pressure to control levels also returned left ventricular filling pressure and ST segment elevation to near pre-nitroglycerin values. The reversal of the beneficial effects of nitroglycerin by phenylephrine suggests a major benefit of nitroglycerin is due to a reduction in left ventricular afterload. *(Come PC, Flaherty JT, Baird MG et al: Reversal by phenylephrine of the bacterial effects of intravenous nitroglycerin in patients with acute myocardial infarction. NEJM 293: 1003-1012, 1975)*

Bacteriologic Aspects of Epidural Analgesia

FRANCIS M. JAMES, III, MD*
RICHARD H. GEORGE, MB, ChB, MRCPath†
HAMID NAIEM, MB, BS, MRCOG‡
GARY J. WHITE, FIMLT§

The incidence of contamination of catheters and syringes used during epidural analgesia for parturients and the effectiveness of bacterial filters were investigated. The effect of bupivacaine on bacterial viability and growth was also studied. Syringes in 5/101 cases were contaminated, while catheter tips located in the epidural space were sterile. Organisms isolated were skin commensals and probably originated on the hands of anesthetic personnel. Bupivacaine (0.25%) was bacteriocidal to *S epidermidis* and *Corynebacterium* spp at 37 C but not at room temperature. These findings illustrate the efficacy of using bacterial filters during continuous epidural analgesia. New syringes should be used for each epidural injection as insurance against seeding of bacteria in the presence of a defective filter.

EPIDURAL analgesia is used in general surgery, obstetrics, peripheral vascular disease, and pain management. Prolonged or intermittent analgesia is achieved by placing a plastic catheter in the epidural space. Attending physicians concerned about the danger of infection from prolonged presence of catheters have questioned the practice of continuous epidural analgesia. Past studies have demonstrated that intravenous cannulae, central venous pressure catheters, and syringes all may be sources of infection.[1-4] In 1962, Barreto[5] found bacterial contamination in 3/35 epidural catheter tips, and Edwards and Hingson[6] reported an epidural abscess following caudal analgesia.

Epidural analgesia is used for approximately 2000 deliveries a year at the Birmingham (England) Maternity Hospital, where it is standard practice to place a bacterial filter* between the hub of the epidural catheter and the local-anesthetic syringe. We investigated the incidence of contamination of syringes and catheters used in epidural analgesia and the effectiveness of the bacterial filter.

*Millex® disposable filter unit, US Pat 3471019, Millipore SA 78 Buc, France.

METHODS

Syringes and epidural catheters used for analgesia during labor in 101 subjects were examined. All catheters were placed in the lumbar epidural space, using careful sterile technic. Anesthesiologists washed their hands and donned plastic apron, cap, mask, and sterile gloves prior to beginning the procedure. The patient's back was cleansed carefully with 2.5% iodine solution and draped in sterile fashion. After identification of the epidural space, a polyvinylchloride catheter was advanced 5 to 10 cm past the epidural needle tip and the needle removed.

The skin was sprayed with plastic dressing, sterile gauze sponges were placed about the catheter, and both sponges and catheter were covered with plastic adhesive tape.

*Associate Professor of Anesthesia, Department of Anesthesia, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina 27103.

†Consultant, Department of Bacteriology, Birmingham Maternity Hospital, Birmingham, England.

‡Research Fellow, Department of Anaesthetics, Birmingham Maternity Hospital.

§Chief Technician, Department of Bacteriology, Birmingham Maternity Hospital.

Paper received: 7/28/75
Accepted for publication: 8/13/75

Next, a bacterial 0.22 μm filter through which all local anesthetic solutions were injected was connected to the hub of the epidural catheter. Following a 2-ml test dose of 0.5% lidocaine hydrochloride, analgesia was established with intermittent 8 to 12 ml doses of 0.25 to 0.5% bupivacaine hydrochloride.

At the Birmingham Maternity Hospital, the same 10-ml plastic syringe is often used for local anesthetic administration throughout labor and delivery. We did not attempt to influence whether or not syringes were changed, but the original syringe was marked for subsequent identification. All syringes cultured had been used at least once. After delivery, syringes and catheters were examined for bacterial contamination. Syringes were cultured by aspirating 10 ml of nutrient broth through a sterile 21-gauge needle from a sterile universal container. The broth was drawn 1 - 2 ml past the 10 ml mark on the syringe, gently swirled about, and reinjected into the sterile container.

We attempted to prevent contamination of epidural catheters during removal from the patient's back. After removing the plastic tape and gauze sponge dressing, the skin about the epidural catheter was cleansed with 70% alcohol and allowed to dry. Sterile gloves were worn while withdrawing the catheter, one hand holding the catheter at its point of entry into the skin, the other grasping the distal portion as it was withdrawn from the back. We cut the catheter into two portions, placing each segment in a separate sterile container.

The first 2-cm section of catheter was not cultured, to decrease the chance of isolating bacteria from the skin entry site. The next 4 to 6-cm segment was labeled "A." The distal 4 to 6 cm, "B," represented the catheter tip, which had been located primarily in the epidural space. In the laboratory, 10 ml of nutrient broth were added to the catheter samples, which were then shaken mechanically for 10 minutes to suspend the bacteria. Syringe and catheter specimens were cultured to isolate and enumerate bacterial contaminants. A loopful of broth from all samples was cultured at 37 C on 5% horse-blood agar and MacConkey agar (Lab M), under aerobic conditions, and 5% blood agar anaerobically with 5% added carbon dioxide.

Further samples were cultured at room temperature on blood agar and MacConkey agar. A 1-ml sample was withdrawn aseptically from each container, mixed with molten cooled agar (oxide blood agar base #2) and a pour plate made. Additional pour plates were made from broth diluted 10^{-1} and 10^{-2}. All plates were incubated for 48 hours. If heavy growth occurred in the pour plates, the residual broth, which had been refrigerated overnight, was serially diluted tenfold to 10^{-5} and further pour plates made to determine the viable count. The remainder of the broth from samples showing no growth was incubated for 48 hours to detect low levels of contamination.

Gram-positive cocci which fermented glucose and produced catalase but not coagulase or deoxyribonuclease were classified as *Staphylococcus epidermidis,* and nonmotile, nonsporing gram-positive bacilli which grew on tellurite medium, fermented glucose, produced catalase but not oxidase, and were not acid fast, were classified as *Corynebacterium* species.

Finally, we determined the ability of bacterial isolates to survive in 0.25% bupivacaine at 37 C and room temperature. Broth cultures of the organisms in the stationary phase were centrifuged and washed 3 times in warm saline solution, then suspended in warm saline to approximately 10^{-6} organisms/ml and 0.025 ml of the suspension was added to 5 ml of bupivacaine solution at the appropriate temperature. After mixing, a sample was immediately withdrawn, serially diluted tenfold, and pour plates made. The mixture was sampled in the same way after 3, 5, and 24 hours.

RESULTS

In 67/101 cases, the same syringe was used for all epidural injections, while in 34/101 it was changed at least once. Five syringe cultures were positive, 3 in original syringes and 2 in syringes changed at least once during the analgesic period. Contamination of 2 of these was detected only by incubating the original broth, but on 3 occasions, the total number of viable organisms was very high (table 1) and heavy growth occurred on the related plates. The total number of viable bacteria was deduced by increasing the viable count per milliliter tenfold. The organisms involved, recognized skin commensals, are listed in table 1.

A mean of 4.6 epidural injections were given in the 5 cases where syringes were later noted to be contaminated. This figure was 4.7 for the entire series of 101 patients. One catheter segment "A" was positive for

TABLE 1
Positive Culture Results of Syringes and Catheters

Syringes

Patient	Original syringe	Epidural injections	Organism identity	Viable count
32	No	12	*S epidermidis*	5×10^5
68	No	4	*S epidermidis*	< 9
71	Yes	2	*S epidermidis*	< 9
94	Yes	3	*S epidermidis*	2.5×10^6
99	Yes	4	*Corynebacterium spp*	2.5×10^6
			Catheter (segment A)	
62	Yes	4	*S epidermidis*	< 10

less than 10 *S epidermidis* organisms. This patient (#62, table 1) received 4 epidural injections with the original syringe. Both the syringe and catheter segment B used in this patient were sterile. All other catheter specimens were sterile. The average epidural indwelling catheter time was 18¾ hours.

Alterations in the viable count of the isolates from patients 32, 94, and 99, when incubated at room temperature and at 37 C in 0.25% bupivacaine, are shown in table 2. Bupivacaine was bactericidal to all 3 isolates at 37 C, causing a five-fold and 25-fold decrease in the count, respectively, within 5 hours. At room temperature, the count in 2 strains apparently increased within the first 3 hours but subsequently fell. However, the bacteria still persisted in large numbers.

DISCUSSION

Bacterial filters of 0.22 μm mesh are capable of preventing passage of bacteria even in the presence of heavy contamination. We did not study a control group without bacterial filters, believing this to be unethical since the use of such filters is standard practice at the Birmingham Maternity Hospital. The bacteria cultured from 5/101 syringes used to inject local anesthetic are skin commensals, probably originating from the hands of injecting personnel. On 3 occasions, the level of contamination was surprisingly high. All broth used to sample syringes had previously been checked for sterility. However, multiplication may have occurred during the handling process and in early stages of refrigeration, raising the original count.

Blogg's group[4] showed that at least 50% of plastic and 100% of glass syringes can be contaminated when used more than once. In studying 50 such syringes from an intensive care unit, they noted a 10% incidence of syringe contamination, while the figure for syringes used similarly in operating rooms was 6%. Our 5% incidence is close to this figure and might be explained by the more careful aseptic technic generally employed in operating room and labor areas.

We have not demonstrated that syringes used once are less likely to be contaminated than those used multiple times, but rather that once used, the incidence of syringe contamination is significantly high enough (5%) to warrant using a fresh sterile syringe for each injection. In our series, original syringes were reused throughout the period of epidural analgesia in two thirds of cases. This is common practice in many labor and operating suites, but we feel it should be abandoned for continuous epidural analgesia.

In a study showing bacterial contamination of 3/35 epidural catheter tips, Barreto[5]

TABLE 2
Alterations in Viable Count of Bacterial Isolates Cultured in 0.25% Bupivacaine HCl

	Isolate*	0 hours	3 hours	5 hours	24 hours
Room temperature	Pt #32	1.7×10^6	4.4×10^6	1.1×10^6	1.5×10^5
	94	5.6×10^6	5.76×10^6	4.25×10^6	1.2×10^5
	99	1.02×10^6	2.7×10^6	8×10^5	1×10^5
37 C	32	1.6×10^6	1.4×10^6	1.52×10^5	0
	94	5.25×10^6	2.7×10^6	2×10^5	0
	99	1×10^6	1.6×10^6	2×10^5	0

*Syringes 32 and 94, *S epidermidis*; 99 *Corynebacterium spp.*

assumed in 2 cases that since the organisms were skin flora, they resulted from seeding of the catheters at the site of entry during withdrawal. In the third case, after the dressings were removed the catheter was found lying on skin outside the epidural space.

In our studies, we cleansed the entry site with 70% alcohol before catheter removal, to reduce potential contaminants, discarding the first 2 cm of catheter, as described. In patient #62 (table 1), segment "A" was probably contaminated at the culture site during catheter withdrawal, while segment "B" and the syringe were negative. This suggests the possibility that positive catheter tips in Barreto's study resulted from skin contamination on withdrawal, but the bacteria may also have originated in contaminated syringes, since Barreto did not mention using bacterial filters nor does he discuss the degree of catheter contamination. In the absence of a filter, the number of contaminating bacteria is obviously of importance, as large inocula are more likely to produce infection.

Whether the increased bacterial count in bupivacaine at room temperature represents division into small cell types or active multiplication is as yet uncertain; further studies now in progress will be reported later. In practice, bacteria within the syringe would not be in contact with anesthetic solution for long, as the syringe is emptied completely immediately after refilling, only a small amount of fluid remaining within the nozzle.

The bactericidal effect of bupivacaine at body temperature is reassuring, for it would help to maintain catheter sterility. Procaine hydrochloride and lidocaine have also been shown to possess antimicrobial activity.[7] However, once bacteria succeed in reaching the epidural space, local anesthetics may actually compromise defense mechanisms; Cullen and Haschke[8] demonstrated *in vitro* that lidocaine has a toxic effect on human leukocytes, significantly inhibiting phagocytosis and metabolism. The toxic effect occurs at a concentration of anesthetic lower than that causing antimicrobial activity.

Recently, attention has been called to the possibility of injecting glass particles into patients after aspirating solutions from ampules.[9,10] As bupivacaine for epidural analgesia is supplied in glass ampules, bacterial filters provide an additional advantage by diminishing the danger of injecting glass particles into the epidural space.

Our findings concur with those of Blogg's group[4] in demonstrating the problem of contamination when syringes are used more than once. Although we have not proved that catheter contamination would have occurred in the presence of contaminated syringes if microfilters were not used, the finding of a 5% rate of syringe contamination should encourage the practice of placing an effective bacterial filter between injecting syringes and epidural catheters.

We recommend that bacterial filters be used in all cases of continuous epidural or continuous spinal analgesia. Since a filter may be defective, we recommend that syringes should be changed between each epidural injection. If these precautions are used and careful aseptic technic is followed in initial catheter placement, there is little chance of bacterial contamination of the epidural space.

REFERENCES

1. Collins RN, Braun PA, Zinner SH, et al: Risk of local and systemic infection with polyethylene intravenous catheters. N Engl J Med 279: 340-343, 1968

2. Erwin P, Strickler JH, Rice CO: The use of polyethylene tubing in intravenous therapy for surgical patients. Arch Surg 66:673-678, 1953

3. Druskin MS: Bacterial contamination of indwelling intravenous polyethylene catheters. JAMA 185:966-968, 1963

4. Blogg CE, Ramsay MAE, Jarvis JD: Infection hazard from syringes. Br J Anaesth 41:260-262, 1974

5. Barreto RS: Bacteriological culture of indwelling epidural catheters. Anesthesiology 23:643-646, 1962

6. Edwards WB, Hingson RA: Present status of continuous caudal analgesia in obstetrics. Bull NY Acad Med 19:507-518, 1943

7. Schmidt RM, Rosenkrantz HS: Antimicrobial activity of local anesthetics: lidocaine and procaine. J Infect Dis 121:597-607, 1970

8. Cullen BF, Haschke RH: Local anesthetic inhibition of phagocytosis and metabolism of human leukocytes. Anesthesiology 40:141-146, 1974

9. Furgang FA: Glass particles in ampules. Anesthesiology 41:525, 1974

10. Katz H, Borden H, Hirsher D: Glass-particle contamination of color-break ampules. Anesthesiology 39:354, 1973

Resection of Stenotic Trachea: A Case Presentation

C. PAUL BOYAN, M.D.*
PAUL A. PRIVITERA, CRNA†
Richmond, Virginia‡

Tracheal stenosis is usually a complication of prolonged mechanical ventilation. If the narrowing is severe it will greatly obstruct the air flow. Resection of the damaged trachea is a life saving procedure. The anesthetic management of the resection of an "ice cream cone narrowing" of the trachea (3 mm diameter) 4 cm above the carina is reported. A forced vital capacity loop (expiration-inspiration) of air flow versus volume revealed preoperatively little difference in the flow during the forced (F-V) and resting ventilation (Vt), thus confirming a diagnosis of severe upper airway obstruction. A total obstruction of the air flow was encountered during the skeletonization of the trachea and the surgeon was allowed to work for not more than 60 seconds at a time. Perfect cooperation between the surgeon and the anesthesia team is necessary for the successful completion of this type of surgery.

STENOSIS of the trachea is seen most often, and is usually due to long-lasting mechanical ventilation, in intensive-therapy patients requiring tracheostomy or prolonged endotracheal intubation. The following case describes the management of anesthesia for resection of a large segment of a stenotic trachea.

CASE REPORT

A 46-year-old obese (94.8 kg) Caucasian man was admitted on 9/24/73 to the hospital with a diagnosis of acute respiratory and congestive heart failure. Past medical history showed chronic bronchitis, emphysema, repeated lung infections, diabetes mellitus (controlled by diet), myocardial infarct (1970), and polycythemia. In spite of nasal O_2 and drug treatment, his situation deteriorated. At this time, blood gases were Pao_2 36 torr, Sao_2 65%, $Paco_2$ >100 torr, pH 7.34, base excess >+16, and HCO_3^- >50. He was intubated and ventilated mechanically for 7 days. With intensive treatment, he gradually recovered and was discharged improved after 18 days of hospitalization.

One month after the prolonged endotracheal intubation, he was readmitted with audible stridor and pronounced dyspnea at rest, unable to breathe adequately even with increased inspiratory and expiratory efforts, and "tugged for breath." Therapy with aminophylline, meperidine, and O_2 by nasal cannula produced slight relief. Tomograms of the trachea demonstrated a tapered 5 cm narrowing of the trachea, 4 cm of normal trachea present between the lower end of the structure and the carina. Bronchoscopy under local anesthesia showed "ice cream cone" narrowing of the trachea beginning 8 cm below the vocal cords.

Four hours after bronchoscopy, the patient developed respiratory difficulty. Blood gases were Pao_2 80 torr, Sao_2 88%, pH 7.07, $Paco_2$ 88 torr, HCO_3^- 24. With proper treatment, the patient recovered, although still having difficulty moving air in and out.

*Professor and Chairman, Department of Anesthesiology, Medical College of Virginia.

†Clinical Director, School for Nurse Anesthetists, Allied Health Professions.

‡Virginia Commonwealth University, Richmond, Virginia 23298.

Paper received: 6/2/75
Accepted for publication: 7/31/75

A forced vital capacity loop (expiration-inspiration) of air flow versus volume revealed little difference in the flow during forced (F-V) and resting ventilation (Vt), confirming the diagnosis of fixed upper-airway obstruction (fig 1). Resection of the stenotic trachea with primary anastomosis was proposed.

On the day of operation, the patient was premedicated with 50 mg of diphenhydramine HCl and 0.8 mg of atropine. The surgeons and the anesthesia team agreed to constant communication throughout the operation. The patient was preoxygenated with 100% O_2 for several minutes and then induced with 300 mg of sodium thiopental. Succinylcholine (100 mg) provided sufficient muscle relation for uneventful intubation with a plastic 9 mm cuffed endotracheal tube, placed above the constriction (fig 2). Tidal exchange of 800 ml was achieved with 30 torr normal pressure over 4 to 5 seconds and the expiratory phase was the same. Anesthesia was maintained with halothane 0.5 to 1.5%, with supplemental doses of d-tubocurarine and morphine. Midline sternal incision provided good access to the trachea.

Surgical retraction and manipulation to free the trachea from adhesions caused total obstruction of ventilation; therefore, after several inflations of the lung with 100% O_2, the surgeon was allowed to work for not more than 60 seconds. Lungs were ventilated again with 100% O_2, followed by more operative procedure. This pattern of ventilation and occlusion was maintained for 20 minutes. At times it was necessary to increase positive pressure in the breathing bag to as high as 60 torr to secure sufficient tidal volume. After the lower part of the trachea was freed, the distal normal section was severed, and a sterile wire-spiral cuffed tube attached to sterile corrugated tubing was introduced into the tracheal stump by the surgeon. The balloon was inflated and the semiclosed system was reestablished (fig 3). The original orotracheal tube was pulled up above the upper end of the tracheal stenosis. After the stenotic area (circa 5 cm) was resected and the posterior healthy parts of the trachea were approximated with nylon stitches, the original endotracheal tube was pushed down and replaced the outside tube, introduced by the surgeon, in the lower end of the trachea above the bifurcation (fig 4).

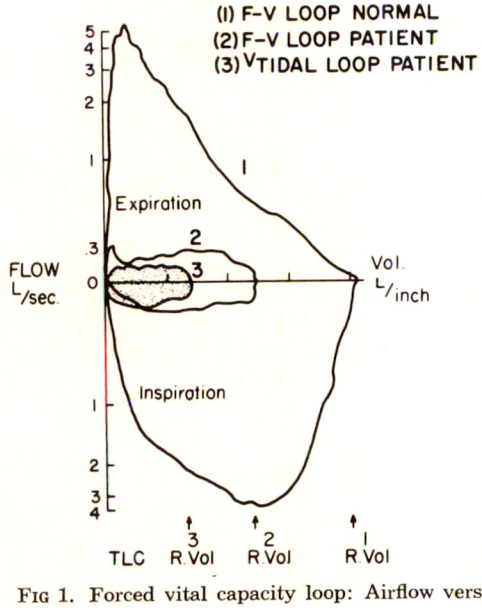


FIG 1. Forced vital capacity loop: Airflow versus volume.

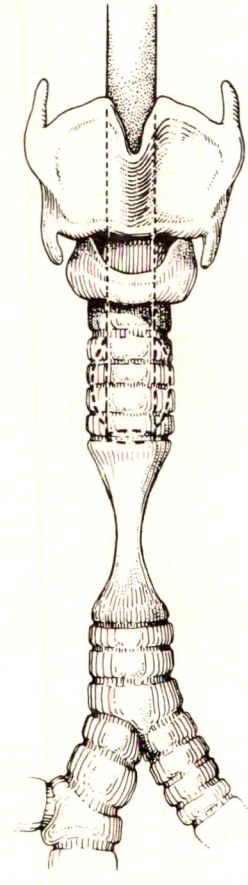


FIG 2. Intubation to stenotic portion of trachea.

The end-to-end anastomosis was completed around the endotracheal tube and required extreme flexion of the head. The

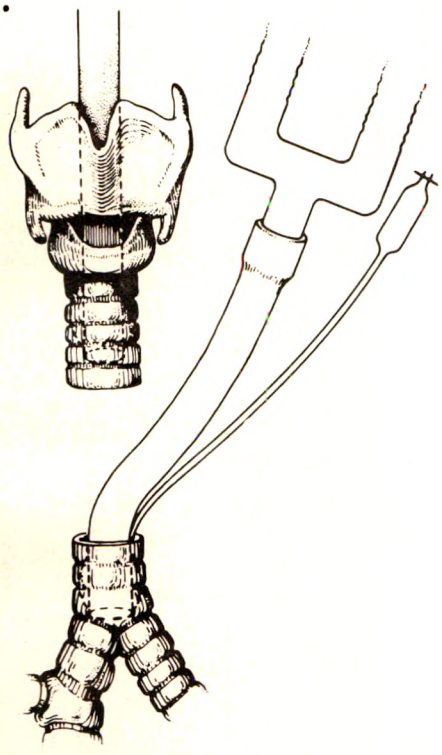


FIG 3. Resection of stenotic trachea.

operation lasted 6 hours. The pathologic specimen was 4.5 cm long and showed a cylindrical stenosis of 3 mm in diameter (fig 5).

The patient was maintained on a ventilator with endotracheal tube for 24 hours. On the 2nd postoperative day, blood gases while the patient was receiving O_2 (3 L) via nasal cannula were Pao_2 66 torr, Sao_2 92%, $Paco_2$ 47 torr, pH 7.38, HCO_3^- 26.9. Postoperatively, the patient developed some atelectasis and pleural effusion at the left lung base. He was discharged much improved on the 21st postoperative day. A 24-month follow-up found him well recovered and working full time at his gasoline station.

DISCUSSION

Tracheal stenosis as a complication of prolonged intubation and mechanical ventilation is a crippling disease which restricts physical activities. Any additional tracheobronchial infection will dangerously aggravate the existing situation. Such narrowing of the trachea (3 mm) as in this patient imposes severe obstruction to the air flow. The forced vital capacity flow-volume loop (fig 1) showed a great reduction in the initial flow of exhalation as compared to normal (0.3 L/sec to 5.5 L/sec). This flow was maintained throughout the entire phase at the same reduced level, demonstrating a constant obstruction by the stenotic area. The same was true for the inhalation phase.

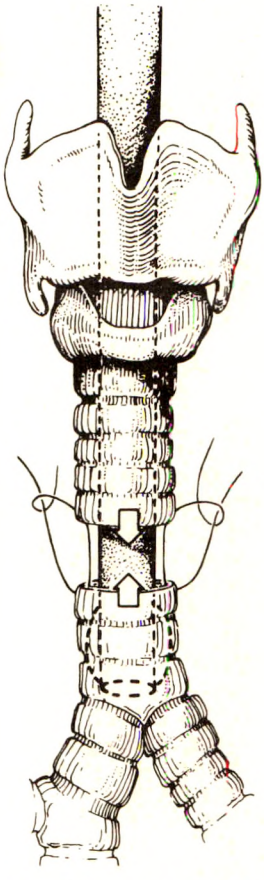


FIG 4. Postresection anastomosis of trachea, with intubation.

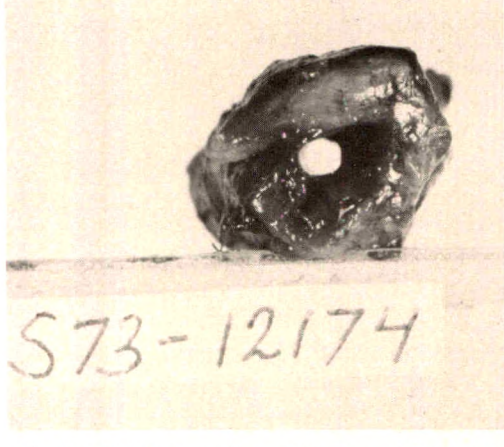


FIG 5. Histologic section of trachea (4.5 cm with 3 mm passage).

Peak flow was greatly reduced but was maintained at the same level throughout exhalation, thus confirming the existence of constant obstruction to the air flow. Miller and Hyatt[1] have suggested that the flow-volume plot of a forced expiratory and inspiratory vital capacity maneuver may be helpful in detecting airway obstructions. Patients having such a tracheal obstruction breathe slowly because they cannot rapidly increase their tidal volume despite additional muscular efforts.

The resting Vt-loop in this patient showed the same restriction in peak flow in both phases with sustained flow throughout the inhalation-exhalation cycle. This type of ventilation requires additional and constant muscular efforts, leading to dyspnea even at rest. The slightest edema of the tracheal mucosa will have similar effects on the air flow by further decreasing the diameter of the obstruction.

In this patient, perfect cooperation between the surgical and anesthesia teams was achieved. The dangerous points during the anesthetic management were complete obstruction during the dissection of the trachea and concern if such an obstruction cannot be relieved by eliminating retraction or any other pressure on the trachea. If the last situation were to occur, the trachea below the obstruction, although not properly dissected, should be opened and a sterile endotracheal tube inserted by the surgeon. Even though this is not the best approach to preserve as much as possible of normal trachea, it is lifesaving.

We were able to ventilate our patient at intervals during the dangerous period of dissecting the trachea and the surgeon desisted from manipulation at the end of 60 seconds, as agreed upon, thus relieving the obstruction. Postoperative care was complicated by having extreme head flexion to reduce the tension at the suture line due to resection of a large segment of the trachea.

In this patient, the endotracheal intubation causing the severe tracheal stenosis had lasted for 7 days, and it took less than a month to develop this life-threatening respiratory complication.

Similar anesthetic technics have been reported by others.[2-5]

REFERENCES

1. Miller RD, Hyatt RE: Obstructing lesions of the larynx and trachea: clinical and physiological characteristics. Mayo Clin Proc 44:145-160, 1969

2. Grillo H, Bendixen H, Gephart T: Resection of the carina and lower trachea. Ann Surg 158:889-893, 1963

3. Geffin B, Bland J, Grillo HC: Anesthetic management of tracheal resection and reconstruction. Anesth & Analg 48:884-894, 1969

4. Corts FE, Smoak LR, Brown LL: Management of tracheal stenosis. J Am ANA 41:541-543, 1973

5. Hogg CH, Benfield JR, Costley DO: Anesthesia for intrathoracic resection of trachea. Am Surg 38:227-230, 1972

RESPIRATORY EFFECTS—LORAZEPAM The ventilatory response before and after intramuscular lorazepam 1.3 and 4 mg, pentobarbital 50 and 150 mg and pentazocine 30 mg was measured in volunteers. Pentazocine produced the greater ventilatory depression followed by pentobarbital 150 and then 50 mg. Lorazepam did not produce ventilatory depression despite production of sedation. *(Gasser JC, Kaufman RD, Bellville JW: Respiratory effects of lorazepam, pentobarbital, and pentazocine. Clin Pharm Ther 18:170-174, 1975)*

Factors Influencing Choice Between Tracheostomy and Prolonged Translaryngeal Intubation in Acute Respiratory Failure: A Prospective Study

MOUSTAFA EL-NAGGAR, MD*
SESHADRI SADAGOPAN, MD†
HARRY LEVINE, PhD‡
HARVEY KANTOR, MD§
VINCENT J. COLLINS, MD‖
Chicago, Illinois**

One of the problems of prolonged ventilatory therapy in acute respiratory failure (ARF) is the need to choose between tracheostomy after 48 to 72 hours of translaryngeal (TL) tracheal intubation or the continuous use of the TL tube for a period of 10 days. Too often the choice has been based on retrospective studies or personal preference. To investigate this problem prospectively, 52 adults in ARF were divided sequentially into 2 groups on their 3rd day of TL intubation. Patients in group I (G-I) retained the TL tube for a total of 11 days; those in group II (G-II) were tracheostomized on the 3rd day. The following factors were used to evaluate the efficiency and complications in each group: patient's epidemiologic variables, daily pulmonary functions, severity of respiratory infections, and scores of post-intubation airway lesions.

No consistent statistically significant differences between the two procedures were seen in the pulmonary functions or the range of individual patient variables. However, with an early tracheostomy, there was an eightfold greater incidence of contamination of the airway by new organisms, airway lesions were more frequent and severe, and the need for the tracheal tube was extended.

To identify the epidemiologic variables and the pulmonary functions that discriminate between patients with serious airway lesions and those with mild lesions, and to evaluate the ability of these variables to differentiate the patients who died from those who survived, the distribution of all factors was compared in the two categories. The epidemiologic variables separated the patients according to their airway lesions only, while the difference in pulmonary functions was statistically significant only between the patients who died and those who survived.

DURING the past decade, there has been a dramatic change in the type of tracheal tubes used in the management of patients in acute respiratory failure (ARF).[1] In the early sixties, it was realized that an initial tracheostomy was justifiable only when translaryngeal (TL) intubation of the trachea was not possible.[2] It was then common practice to perform the tracheostomy within the following 24 hours, if the need for the tracheal tube continued.[3]

In the late sixties, interest increased in prolonging the period of TL intubation, because of dissatisfaction with the results of tracheostomy in some patients.[4] The complications of transtracheal (TT) intubation,

*Associate Professor of Anesthesiology, Rush-Presbyterian St. Luke's Medical Center, Chicago, Illinois.
†Attending Staff, Department of Anesthesiology,
‡Director of Biomedical Statistics, Department of Surgery.
§Chairman, Division of Infectious Disease.
‖Chairman, Department of Anesthesiology; Associate Professor, Northwestern University.
**Departments of Anesthesiology, Surgery and Internal Medicine, Cook County Hospital, Chicago, Illinois 60612.
Reprint requests to Dr. El-Naggar.
Paper received: 2/21/75
Accepted for publication 7/29/75

fairly frequent and often serious,[5] included bleeding, difficulty in cannulation, dislodgement, generalized surgical emphysema, pneumothorax, tracheal stricture and fistulas, and scar formation. With improvements in construction of tracheal tubes and in the overall management of patients with an artificial airway,[6] clinicians prolonged the duration of TL endotracheal intubation.[7] This practice was also accompanied by complications, such as mucus obstruction, accidental extubation, pneumonia, ulceration of nostrils or nasal septum, hoarseness, cord avulsion-perforation, dislodgement of the tube into the right main bronchus, and tracheal stenosis.

Currently there is no agreement as to the optimum period of TL intubation after which tracheostomy is indicated. Even Lindholm, in an extensive study of prolonged tracheal intubation, affirmed that he could not establish a time limit.[8] Pontoppidan's group[1] retained TL tubes up to 8 days, while Safar[9] recommended tracheostomy on the 3rd day of TL intubation.

The present study was undertaken to compare the efficacy and safety of prolonged TL and TT intubation in adults in ARF and to identify factors that may influence the outcome of therapy.

METHODS AND MATERIALS

On their 3rd day of TL intubation, 52 adult patients in ARF who were judged to require continued intubation for a further period of time were sequentially divided into 2 groups. Patients in group I (G-I) were managed by continued TL airway for a total period of 10 to 11 days, after which tracheostomy was to be performed, if the need for an artificial airway continued. Patients in group II (G-II) were to be tracheostomized on the 3rd day of artificial airway care.* All 52 patients received the same respiratory, general, and supportive care, according to individual needs and the policies and procedures of the general intensive care unit.

Criteria for scoring respiratory infections included vital signs, laboratory findings, and x-rays (table 1). After extubation, patients were examined by a member of the ENT staff, using a Macintosh-blade laryngoscope and a fiberoptic bronchoscope. Pharyngeal, laryngeal, and tracheal lesions were rated according to modified Lindholm scoring system.[8] Epidemiologic variables and respiratory measurements (table 2) were collected daily on computer-coded forms by the second author, who was not in charge of patient care during the study.† Some of the data collected were deleted because of incomplete information, inadequacy of method of determination, or difficulty in statistical interpretation. The Fisher linear discriminant function test was used to quantitate the distribution of the epidemiologic variables in the following groups of patients: (a) patients who had prolonged TL intubation versus those who had an early tracheostomy; (b) patients who had mild airway lesions versus those who had serious lesions; and (c) patients who were extubated versus those who died.

TABLE 1
Score System for Quantification of Respiratory Infections

	Score	Maximum score
A. Clinical evidence		
1. Fever	1	
2. Pulse: 20% increase	1	
3. Respiratory rate: 20% increase	1	
4. Secretions	1	
5. Leukocytosis	1	
Total	5	5
B. Radiologic evidence		
1. Opacification, segment	1	
2. Opacification, one lobe	2	
3. Opacification, one lung	3	
Total	6	5
C. Laboratory evidence of pathogens in tracheal aspirate	5	5
Total	16	15

Student's *t*-test and analysis of variance were used to derive the significance of the differences between the mean values of repiratory measurements per day of management in the different groups. Statistical significance was obtained at the 0.05 level.

RESULTS

A. Prolonged Translaryngeal Intubation Versus Early Tracheostomy. — The linear

*Both TL and TT intubation employed portex low-pressure cuffed tubes.

†Coded forms available on request from Dr. El-Naggar.

TABLE 2
Epidemiologic and Respiratory Variables Recorded

1. Treatment { Prolonged TL / Early TT
2. Outcome { Extubated / Expired
3. Airway lesions { Mild (scores 0, 1, or 2) / Serious (scores 3)
4. Age, yr
5. Sex { Male / Female
6. Race { Black / Caucasian
7. Smoking { Yes / No
8. Alcohol intake { Yes / No
9. Narcotic habituation { Yes / No
10. Steroid medication { Yes / No
11. Indication for intubation
    a. $Paco_2 > 50$ torr
    b. $Pao_2 < 50$ torr
    c. Respiratory rate > 35 min
    d. Secretions
    e. Maintain a free airway
12. Mode of ventilation
    a. Assisted
    b. Controlled
    c. Assisted/controlled
13. Duration of tracheal intubation by
    a. TL tube
    b. TT tube
14. a. Internal diameter of TL tube (mm) 7, 8, and 9
    b. size of TT tube (French) 33, 36, 39
15. Number of attempts at TL intubation
16. Route of TL intubation { Nasal / Oral

Respiratory Measurements

1. Bacteriologic study of tracheal aspirate.
2. Score of airway lesions.
3. Score of respiratory infections (RI).
4. Alveolar-arterial O_2 tension difference with 100% inspired O_2 $P_{(A-a)}$ O_2 (100%)
5. Ratio of dead-space volume to tidal volume (V_D/V_T x 100)
6. Tidal volume (TV).
7. Forced vital capacity (FRC).
8. Effective dynamic compliance (EDC).

discriminant analysis test yielded an f $(16.35) = 1.31$; p value > 0.25. This indicated that the epidemiologic variables were equally distributed between the TL and TT groups. The type and frequency of organisms newly identified in daily examined tracheal aspirate was similar during the first 4 days of management G-I and G-II. However, between the 4th to 11th days, there was an 8-fold increase in the number of newly identified organisms in G-II in comparison to G-I (table 3).

The mean score for airway lesions/day of management (fig 1) was significantly higher in G-II than in G-I ($p < 0.05$). The 26 patients in G-II had an average score of 1 for the lesions evaluated when these patients were tracheostomized on the 3rd day of TL intubation. This same score in G-I was observed on the 7th and 8th days. Because the patients in G-II were managed by two types of tubes, the average score on the 3rd day was added to that on subsequent days (fig 1). The combined scores of airway lesions in G-II were also significantly higher ($p < 0.01$) than in G-I.

In a comparison of the percentages of the cumulative number of patients extubated or expired and the number of patients being treated in G-I or G-II at the specific day of management (fig 2), analysis of variance test showed the difference in these percentages between the expired patients in G-I and G-II were statistically insignificant,

TABLE 3
Frequency of Newly Identified Organisms in Aerobic Cultures of Tracheal Aspirate During Study Period

Type of organism	Group I	Group II
Hemophilus influenzae	2	4
Escherichia coli	5	6
Klebsiellae	2	10
Pseudomonas aerogenosis	4	9
Herella	1	1
Candida	1	0
Diplococcus pneumoniae	1	0
Proteus mirabilis	2	0
S aureus	0	4
Streptococcus	0	1
Total	18	35
Number of organisms 1st identified on 1st day	3	5
Number of organisms 1st identified during 1st 4 days	15	19
Number of organisms 1st identified during 3rd to 11th days	2	16

while the higher percentages in the extubated patients in G-I were statistically more significant than those in G-II. These results indicated a significant delay in extubating the tracheostomized patients (G-II), independent of the outcome or duration of therapy.

There were sporadic and inconsistent differences in the means and SD of the respiratory measurements according to day of management. In G-II, with the exception of V_D/V_T ratio determination, there was a significant deterioration in these measured values subsequent to the tracheostomy on the 4th day of management.

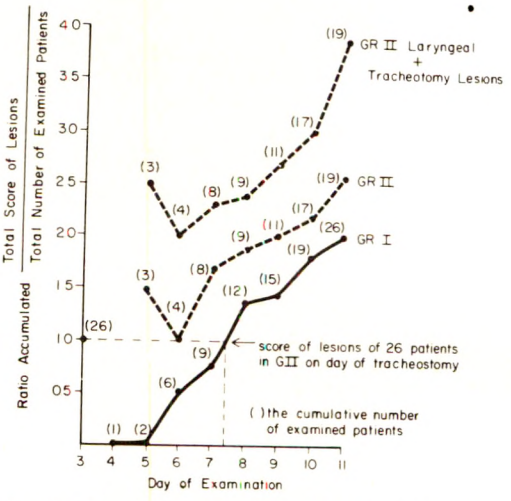


FIG 1. Cumulative scores of airway lesions: ratio of lesions in patients examined per day of examination.

B. Variables that Contribute to Airway Lesions.—Patients with lesions were divided into 2 groups: (A) Those with mild airway lesions (score 0, 1, or 2) and (B) patients with serious airway lesions (score 3 or over).

Linear discrimination analysis showed

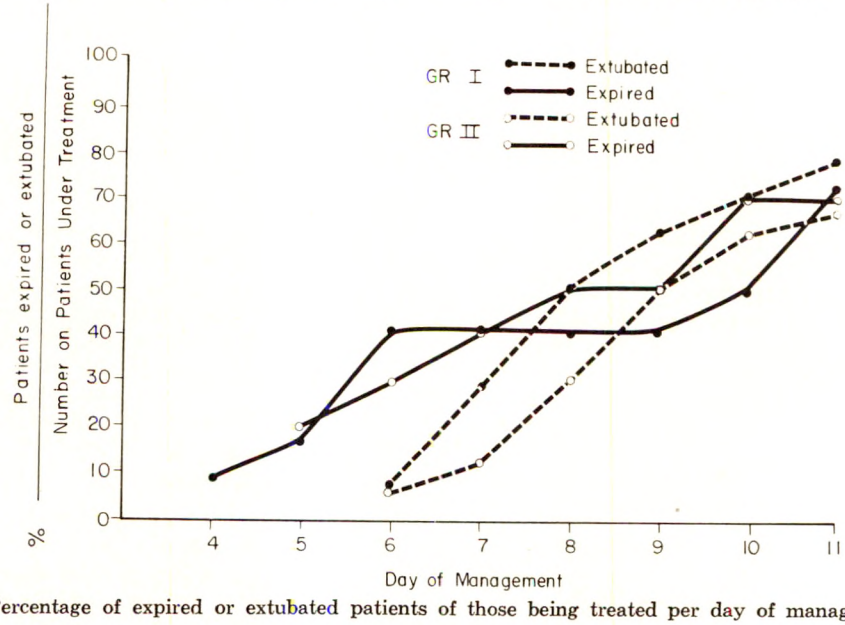


FIG 2. Percentage of expired or extubated patients of those being treated per day of management.

TABLE 4
Variables that Contribute to Airway Lesions (Descending Importance)

1. Use of transtracheal tube
2. Assisted ventilation
3. $Paco_2 > 50$ torr as indication for intubation
4. Duration of translaryngeal intubation
5. Race (Black more prone)
6. Secretions as an indication for tracheal intubation
7. TT tube 36 French
8. Duration of TT intubation
9. $Pao_2 < 50$ torr as indication for intubation
10. Use of steroids
11. Sex (females more prone)
12. TT tube 33 French
13. Smoking
14. TL tube size 8 mm ID
15. Patient extubated

Indecisive Variables Include

1. Initial diagnosis (medical or surgical)
2. Alcohol intake
3. Habituation to narcotics
4. Respiratory rate >35 as indication for intubation
5. Free airway as indication for intubation
6. Duration of TT intubation
7. Number of attempts to intubate trachea translaryngeally

that 15 of 22 variables (table 4) correctly classified 46 patients out of 52 into group A and incorrectly classified 6 patients with mild lesions. The test yielded an $f = 4.33$, with 13 and 38 degrees of freedom, and a p value of <0.001.

There was no significant difference between the mean values of the 6 respiratory parameters (RI, $P_{(A-a)}$ O_2 (100%), V_D/V_T, TV, FVC, or EDC) per day of management or the number or type of positive bacteriologic cultures in the patients who had mild or serious airway lesions.

There was no correlation between the airway lesions at the cuff site and the following factors: (a) duration of intubation; (b) type of tracheal tube; (c) extubation or death; and (d) epidemiologic variables or respiratory measurements.

C. Variables that Influence the Prognosis of Prolonged Tracheal Intubation (death during the study versus extubation).—The 52 patients included in the study were categorized as follows: (1) those who died during the study; (2) those successfully extubated and discharged from the General Intensive Care Unit (GICU). The linear discriminant function test, used to investigate the distribution of the epidemiologic variables between those two categories, yielded an $f\ (16.35) = 0.75$ with 16 and 35 degrees of freedom ($p<0.10$), indicating that the epidemiologic variables could not help predict which patients would die and which would be extubated.

Although there was no significant difference in respiratory measurements on the 1st day of management, in subsequent days significant and consistent differences were observed in the following measured values, in the following order: TV and FVC on the 2nd day, RI on the 3rd day and $P_{(A-a)}$ O_2 (100%) and EDC on the 5th day. The mean values of the V_D/V_T x 100, however, showed no significant difference between the group of patients who died and the group subsequently extubated.

In the expired group, the percent incidence of identified organisms was double that in the extubated patient group, while the prevalence of *E coli, Pseudomonas* species, *Klebsiellae, Hemophilus influenzae,* and *S aureus* was almost 3 times greater.

Mean values of respiratory measurements in the extubated group and expired group on the 1st and last days of management are shown in table 5.

DISCUSSION

In the past, prolonged therapeutic tracheal intubation has been defined as the maintenance of an artificial airway for more than a few hours.[10] This definition is unsatisfactory, due to the common use of intubation in the management of ARF for longer periods.[1,3,9] We chose the period of 3 days to define prolonged intubation, because TL tubes are commonly used in the initial 48 to 72 hours of artificial airway care, while there is no agreement regarding the choice between TL and TT intubation beyond this period.

Advocates of TT intubation on the 3rd day of management claim better removal of secretions, reduction of dead space, and better tolerance by patients.[8] Advantages

TABLE 5
Means and Standard Deviations of Values on 1st Day of Management and Day of Extubation or Death

	Patients survived		Patients died	
	Means and (SD) on 1st day	Means and (SD) on day of extubation	Means and (SD) on 1st day	Means and (SD) on day of death
Number of observations	30		22	
Tidal volume (TV/ml)	269 (117)	409 (105)	213 (101)	188 (34.7)
Forced vital capacity (FVC/ml)	753 (358)	1227 (399)	42 (214)	728 (233)
Effective dynamic compl (EDC/ml/cm H_2O)	21 (6)	36 (8.5)	22 (7.4)	22 (8.8)
V_D/V_T ratio	49 (11.4)	38 (10.3)	50 (10.5)	49 (6.3)
$\triangle P_{(A-a)} O_2$ (100%)	397 (105)	244 (68)	391 (98)	423 (84)
Respiratory infections (RI)	4.3 (2.3)	2.16 (1.9)	4.9 (3)	9 (3.9)

1. There was no significant difference in the 2 groups between mean values on 1st day.
2. Differences between mean values on day of extubation or death in G-I and G-II were highly significant.
3. With exception of scores of respiratory infections, differences between mean values on 1st day and day of death were statistically insignificant. There was a highly significant difference between mean values on 1st day and day of extubation (p 0.005 to 0.001)

claimed for TL intubation for over 3 days include better tube stability and tracheal alignment, absence of a surgical wound, and less bacterial invasion.

In this prospective study, the differences in the daily respiratory measurements between prolonged TL intubation and an early tracheostomy were only sporadically significant. This indicated that the TL and TT tubes were equally efficient in the management of ARF. However, the disadvantages in an early tracheostomy include deterioration in post-tracheostomy pulmonary function measurements, which may not be well tolerated by the unstable patient, and an increase in identified pathogens, which may invite the unnecessary administration of antibiotics. There is also a tendency to delay removal of the TT tube, which increases the cost of patient care and prolongs the risks inherent in artificial airways. In addition, airway lesions (excluding those related to the cuff) in early tracheostomized patients not only showed significantly higher scores but also tended to be delayed and of a more serious nature.

One patient had a granuloma at the tracheostomy site at the time of extubation and was discharged from the hospital for outpatient followup. Two weeks later, he was seen in the emergency room, where he sustained cardiopulmonary arrest due to severe tracheal stenosis. Immediate resuscitation was successful; however, the patient did not regain consciousness and later died. Two more patients who had an early tracheostomy also developed tracheal stenosis; one had a resection anastomosis and the other a permanent tracheostomy. Another patient developed a tracheoesophageal fistula at the tip of the TT that was related to misalignment of the tube.

Two women with status epilepticus showed subglottic cicatrical web formation after 3 days of translaryngeal intubation. Both were successfully treated by dilation.

In our view, the major advantage of maintaining the TL tube for 11 days was the fact that only 10 out of 52 patients needed airway care beyond this period. Thus, 80% of the patients in ARF who required a tracheal tube for 3 days or more could have been spared the tracheostomy procedure.

The airway lesions described in this report were less severe or frequent than those reported by Lindholm[11] and by Hedden's group[12] but similar to those observed by Deane and Mills.[13] The latter investigators found fewer complications in patients intubated more than 100 hours. In our study, there was a linear correlation between the duration of intubation and the severity of the lesions observed. For this reason we recommend limiting the period of translaryngeal intubation to 11 days.

Factors common to patients with serious airway lesions (table 4) suggest that it is

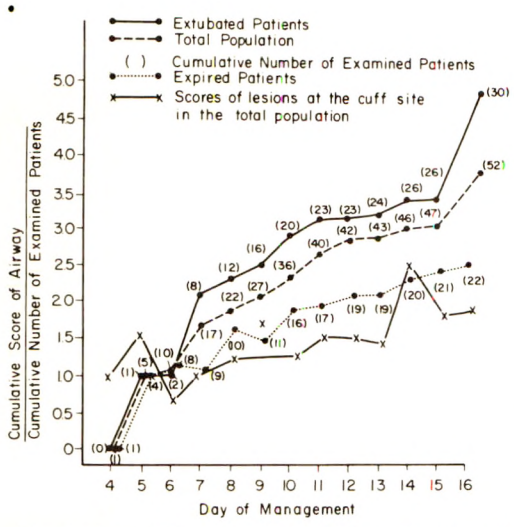


FIG 3. Cumulative scores for lesions per day of management in patients extubated, patients expired, total population of patients examined, and at cuff site.

the degree of friction between the artificial airway and the air passages that is significant. Lesions were more common (1) in patients on spontaneous or assisted ventilation, where friction is unavoidable; (2) in patients who survived (fig 3); and (3) in the 2 patients in status epilepticus. Unexpectedly, there was a correlation between steroid administration and serious airway lesions, but no correlation between these lesions and the number of attempts to intubate the trachea. The latter observation agrees with that by Fassolt.[14]

None of the epidemiologic variables or respiratory measurements (table 2) was useful for predicting the outcome of prolonged tracheal intubation for ARF on the 1st day of management, a favorable prognosis depending on improvement in pulmonary function. A poor prognosis was associated not only with lack of improvement in these measurements but also with an increased score in respiratory infections (table 5).

ACKNOWLEDGMENT

The authors wish to acknowledge with thanks the cooperation of the staff of the GICU, the Department of Surgery, and the ENT Division of Cook County Hospital.

REFERENCES

1. Pontoppidan H, Geffin B, Lowenstein E: Acute respiratory failure in the adult (part 3). N Engl J Med 287:799-806, 1972

2. Allen TH, Steven IM: Prolonged endotracheal intubation in infants and children. Br J Anaesth 37:566-573, 1965

3. Proctor DF, Safar P: Management of airway obstruction (chapter 3), Respiratory Therapy. Edited by P Safar. Philadelphia, FA Davis Company, 1965, pp 30-69

4. Lancet: Leading article 1:258, 1967

5. McClelland RMA: Complications of tracheostomy. Br Med J 2:567-569, 1965

6. Stetson JB: Introductory essay: Prolonged Tracheal Intubation. Edited by JB Stetson. Boston, Little, Brown and Company. Int Anesthesiol Clin 4:767-779, 1970

7. Freeman GR: A comparative analysis of endotracheal intubation in neonates, children and adults. Complications, prevention and treatment. Laryngoscope 82:1385-1398, 1972

8. Lindholm CE: Prolonged endotracheal intubation. Acta Anaesthesiol Scand Suppl 32:102-109, 1969

9. Safar P: Severe multiple trauma; life support in head-chest injury. Abstracts, The 7th Annual Symposium on Critical Care Medicine, Pittsburgh, 1973

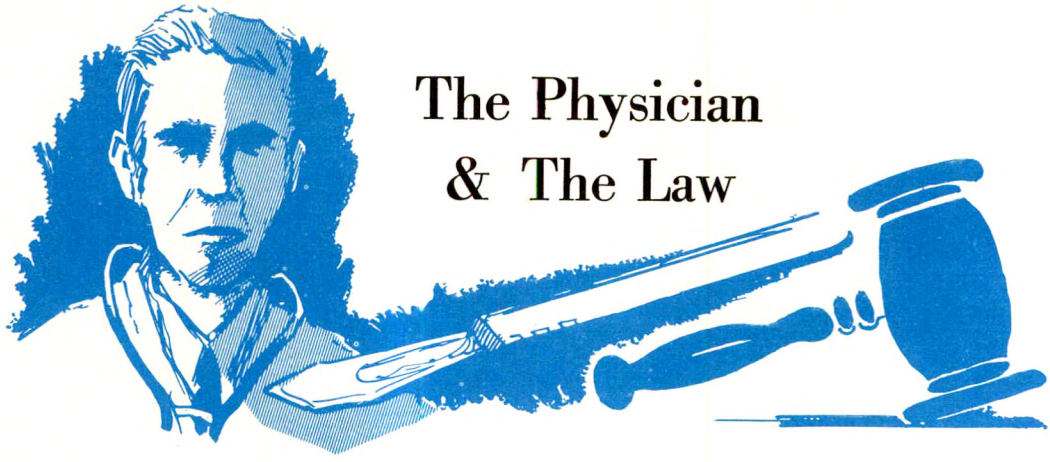
10. Harrison GA, Tonkin JP: Prolonged (therapeutic) endotracheal intubation. Br J Anaesth 40: 241-249, 1968

11. Lindholm CE: Prolonged endotracheal intubation. Acta Anaesthesiol Scand Suppl 32:25-26, 1969

12. Hedden M, Ersoz CJ, Donnelly WH, et al: Laryngeal damage after prolonged use of tracheal tubes in adults. JAMA 207:703-708, 1969

13. Deane RS, Mills EL: Prolonged nasotracheal intubation in adults: a successor and adjunct to tracheostomy. Anesth & Analg 49:89-97, 1970

14. Fassolt A: Post anaesthetic sore throat complaint following the use of various kinds of endotracheal tubes. Anaesthesist 23:62-67, 1974



The Physician & The Law

Anesthetic Manufacturer not Liable for Death of Patient

Two physicians and the manufacturer of an anesthetic were not liable for the death of a patient from a cardiac arrest during surgery, a federal appellate court in Ohio ruled.

The patient had been operated on for removal of a cataract in his right eye. Innovar was administered as an anesthetic agent. During the operation, the patient suffered a cardiac arrest and brain damage and died about two weeks later.

Claiming that the manufacturer was negligent in failing to adequately warn users of the drug of its side-effects and adverse reactions, the patient's widow brought an action against the manufacturer. She also brought an action against the ophthalmologist and the anesthesiologist based on their selection of Innovar and their efforts to resuscitate the patient after his cardiac arrest. A jury found in favor of the physicians and the manufacturer, and the widow appealed.

On appeal, she contended that the trial court improperly permitted the physicians and their experts to testify to their experience with Innovar after the operation. The federal appellate court said that the liability of the manufacturer and the physicians could be measured only by their knowledge of the drug obtained prior to the operation. However, no objection to the testimony by the physicians or their experts was made at trial. The federal court said that the factual issues had been fairly presented to the jury and affirmed the trial court's judgment.—*Daly v. McNeil Laboratories, Inc.*, 509 F.2d 617 (C.A.6, Ohio, Jan. 21, 1975)

*Reprinted with permission from THE CITATION published by the Law Division of the American Medical Association.

Cardiovascular Effects of Cannabinol During Oral Surgery

JOHN M. GREGG, DDS, PhD*
ROBERT L. CAMPBELL, DDS†
KENNETH J. LEVIN, MS, MD‡
JAWAHAR GHIA, MD§
RILEY A. ELLIOTT, BS‖

Fifty-five clinical trials were conducted to determine the cardiovascular combined effects of stressful oral surgery and systemic cannabinols. In a first study, $\triangle^9$-tetrahydrocannabinol (THC) was given IV as a premedicant and compared with diazepam and with a placebo. A classic dose-related tachycardia followed THC injection. The peak heart rate response of patients premedicated with 0.044 mg/kg THC was 24.1% higher ($p<0.05$) than the peak effect for a nonsurgerized control group, suggesting a synergistic effect between THC and surgical stress. A predisposition to syncopal hypotension followed THC premedication, and antiarrhythmic effects were observed after large doses. The injection of local anesthetic preparations containing epinephrine did not alter THC cardiovascular response. An apparent drug interaction was observed, however, in a second study, in patients given general anesthesia within 72 hours after smoking marijuana. These patients demonstrated sustained abnormal postoperative tachycardia when compared with control nonsmokers, an effect which may have resulted from an interaction between stored cannabinol metabolites and atropine administered as part of the anesthetic technic. It was concluded that THC had no particular advantage over diazepam or placebo as a premedicant. Further, THC altered the patients' adaptivity to stress and interacted undesirably with other anesthetic medications.

THE cannabinols, the most heavily used psychoactive drugs in the world, are used by an estimated 250,000,000 persons. The 1972 estimates for college-age users was 54% (with about 5 to 10% of these using marijuana on a daily basis), and 1980 projections for young adults have been set at 66%.[1] Inevitably, more marijuana users will be approaching elective or emergency surgical anesthesia after having "premedicated" themselves with cannabinols.

Marijuana has several properties that suggest it might be useful as a surgical premedicant: analgesia in subhumans;[2] antisialosis;[3] a moderate amnesic effect;[4] a low or nonexistent addiction potential;[5] and a very low toxicity.[5] Death from cannabinol overdose has rarely been reported, and most severe reactions have occurred following uncontrolled IV injections. Extrapolating from animal toxicity studies, a human LD_{50} of at least 30 mg/kg is far above the psychologically effective range, and much more favorable than that of alcohol.[5] And finally, the extensive use of marijuana as a social drug suggests a pleasant psychic experience which could also serve well as a surgical pain and anxiety sedative.

There is considerable evidence, however, that significant incompatibilities may exist

*Associate Professor, Departments of Oral Surgery and Anesthesiology, The University of North Carolina, Chapel Hill, North Carolina 27514.
†Assistant Professor, Department of Oral Surgery, The University of North Carolina.
‡Associate Professor, Department of Anesthesiology, The University of North Carolina.
§Assistant Professor, Department of Anesthesiology, The University of North Carolina.
‖Intern in Dentistry, The University of Vermont.

This study was supported in part by NIH Research Grant DE 02668 from the National Institute of Dental Research and by NIH Grant RR 05333 from the Division of Research Facilities and Resources.
Paper received: 5/13/75
Accepted for publication: 8/7/75

between cannabinol premedication and surgical anesthesia, making this drug of questionable value in this situation. Although the response to marijuana, as to most psychoactive drugs, is largely determined by dose[6] and route of administration,[7] personality factors,[8] psychologic set,[9] and especially the stress of the environmental setting[3,10] appear inordinately significant. For example, dysphoric "high" responses ("highs") with marijuana are more commonly seen in patients with chronic depression,[11] and paranoid delusional reactions occur more frequently in hypnotic-suggestible patients.[12] Marijuana is now looked upon as a mood-intensifying drug rather than as a pure CNS excitant, euphoriant, or depressant per se.[13] Thus, it might be anticipated that the psychophysiologic stress of a surgical experience in the marijuana-premedicated patient could result in an exaggerated sympathoadrenal stress response.

Most of the adverse effects reported for marijuana have been on cardiovascular functions and related drug interactions. As in the present study, the most consistently reported pharmacologic response is a dose-related tachycardia.[14,15] Both hypotensive and hypertensive effects have been described.[16,17] The combination of increased cardiac demand from tachycardia with sustained catecholamine elevation has led some authors to warn that the use of cannabinols in elderly or in cardiac patients may be hazardous.[5,15] Studies of patients with angina pectoris support this warning, for it has been shown that smoking marijuana significantly decreases exercise tolerance when compared to placebo smoking.[18]

Studies of long-term hashish users have demonstrated elevated hemoglobin and packed-cell volumes, which have been attributed to chronic hypoxia.[1,19] There are also reports of increased potential for cardiac arrhythmias,[18] and ECG studies have demonstrated shortening of the S-T interval and depression of T-wave amplitude.[20] Other studies, however, have indicated that cannibinols may actually have a therapeutic or protective effect against cardiac arrhythmias.[21] Nevertheless, because the incidence of arrhythmia during oral surgery with local anesthesia alone has been reported as greater than 45%,[22] our investigations of cannabinol effects appear warranted.

There have been other warnings of dangerous drug interactions between marijuana and anesthetic medications. Cannabinols have been shown to double ketamine sleeping time and to quadruple thiopental duration.[23] Pentobarbital sleeping time in rats was doubled after a single cannabinol dose.[24] Marijuana is also known to potentiate the depressant effects of alcohol[25] and to summate with amphetamines.[26] Beaconsfield's group[14] predicted dangerous cardiovascular drug interactions between marijuana and such common agents as atropine or local-anesthetic preparations containing epinephrine.

Our studies were designed to determine the cardiovascular effects of cannabinols (1) by comparing the cardiovascular effects of premedicant IV doses of THC, diazepam, and placebo, and (2) by a retrospective study of the cardiovascular effects of outpatient general anesthesia in patients known to have smoked marijuana within 72 hours before anesthesia.

STUDY 1: METHODS

Ten healthy male patients between 19 and 28 years of age (mean 26 ± 2.8 yr SD) were selected for study, without regard to prior marijuana experience, from a population requiring elective surgical removal of 4 impacted 3rd molars. All 10 subjects had smoked marijuana, and 2 admitted to previous experiences with LSD-25 and mescaline. After explanation of the procedure and the risks involved, informed consent was obtained. A complete physical examination, including ECG, chest x-ray, and laboratory tests, showed all subjects to be healthy and free of cardiovascular or respiratory abnormalities. Each subject participated in 4 separate weekly clinical trials, at which time a single 3rd molar was removed, and during which time he was premedicated with one of the following 4 agents:

1. THC: 0.044 mg/kg* ("larger dose")
2. THC: 0.022 mg/kg* ("smaller dose")
3. Diazepam: 0.157 mg/kg
4. Placebo (dextrose 5%, NaCl): 0.2%

These were given in random order on 4 consecutive weeks, double-blind with respect to patient and surgeon. This allowed each patient to serve as his own control for measuring cardiovascular changes. The THC solutions were prepared by dissolving the

*These 2 dosages were selected from a pilot study in which 0.02 mg/kg was found to consistently produce minimal subjective "highs" and 0.04 mg/kg consistently produced near-100% "highs." Subjects reported that IV "highs" were equal to or beyond the usual effects from smoking marijuana.

dose of active THC in 0.5 ml of ethyl alcohol and adding 25 ml of human serum albumin.

On the morning of each clinical trial, patients, who had fasted since midnight and had recently voided, were brought to the clinical research unit. All had been asked to avoid smoking in any form for at least 24 hours before each clinical trial. Patients reclined in an approximately 30° sitting position throughout the test period. The ECG was continuously recorded from a modified lead II placed entirely on the thoracic cage, and heart rate was monitored electronically from the ECG. Indirect systolic and diastolic blood pressures were recorded at 2-minute intervals with a Litton phonosensor. All transducer signals were preamplified and oscilloscope-displayed through the Litton Product Basic Bedside Unit. Continuous recording of output was made on a 12-channel Honeywell 5600 electromagnetic tape recorder and subsequently printed out on the Siemens Mingograph® polygraph.

Simultaneously with the cardiovascular monitoring, subjective psychologic drug effects were studied, using the State-Trait Anxiety Inventory (STAI),[27] a modified Subjective Drug Effects Questionnaire (SDEQ),[28] and the measure of subjective "high" described by Perez-Reyes and coworkers.[29] Details of these tests are contained in another report.[30]

Baseline resting physiologic functions were monitored for a 30-minute period, and the injection procedure was isolated and shielded from the patient's view. Patients were told that the injection was to begin, and the premedicant was injected evenly over a 5-minute period through an indwelling venous catheter, after which the surgeon and nurse entered the operatory, where they administered the local anesthetic. Appropriate peripheral trigeminal blocks were performed by standard aspiration technic, using an average of 2 to 4 ml (40 to 80 mg) of 2% lidocaine containing 40 to 60 mcg of 1:100,000 epinephrine. The surgeon then removed the molar by ordinary surgical technics, pacing the procedure to be completed exactly 30 minutes after drug injection. Following a 30-minute surgical test period, the patient remained in the operating chair for an additional 60 minutes of monitoring and then was escorted to a recovery room, where monitoring continued for a minimum of 60 minutes until discharge.

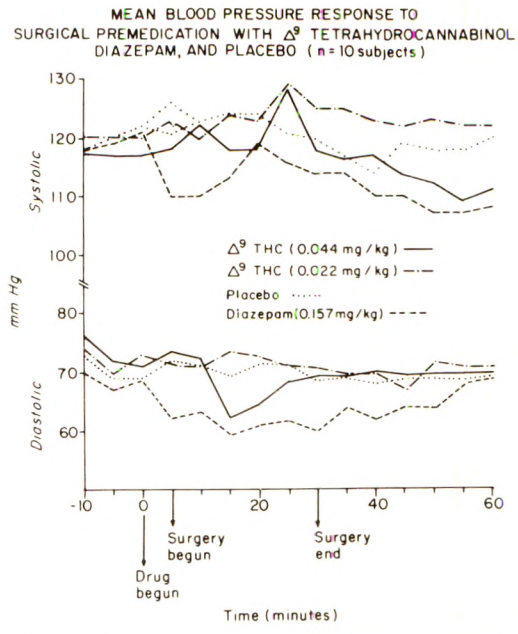


FIG 1. Measures of blood pressure response to surgical premedication with ⁹THC revealed a peak systolic hypertension 25 minutes after injection. A mild gradual hypotensive trend followed the end of surgery with the larger THC dose.

The additional control group of 5 nonsurgerized volunteers consisted of healthy men, aged 21 to 34 (mean 26 ±3.2 SD), who underwent a single trial in which they were given a single dose of THC (0.044 mg/kg) from the batch used in the main experiment described above. Cardiovascular monitoring, subjective measurements, and experimental setting were identical, but no operations were performed. When cardiovascular data from this group were compared with data from the main experiment, influences that could be attributed solely to drug effect could be separated from those due to drug-surgical stress interactions.

STUDY 1: RESULTS

Blood Pressure.—The average blood pressure response to surgical premedication with THC changed little from average preoperative baselines and placebo levels (fig 1). A mild elevation of systolic pressure was observed, with the peak effect at the 25-minute postinjection interval; the larger dose of THC produced an average elevation of 8 torr, and a 9-torr elevation followed the smaller dose. In the larger-dosage THC group, a gradual hypotensive trend was observed, beginning approximately at the time of completion of the operative procedure and reaching an average maximum depression of 12 torr below preoperative baseline

and 14 torr below placebo levels at the 55-minute postinjection time period. Blood pressures following larger doses of THC returned gradually to placebo levels an average of 70 minutes after initial drug injection.

The blood pressure effects of diazepam were dissimilar to those of THC: Diazepam consistently induced a mild systolic hypotension, ranging from 7 to 15 torr throughout the entire trial. However, average diastolic responses to both dosages of THC were statistically and clinically similar to placebo responses throughout.

Transient moderate hypotension of 20 to 45 torr systolic and diastolic in the interval of 4 to 8 minutes after THC injection occurred in 3/10 subjects. These episodes appeared to be typical syncope, associated with nausea, dizziness, anxiety complaints, and, in 2 instances, loss of consciousness accompanied by carpopedal spasm for up to 25 seconds. No similar syncopal responses or transient hypotension was observed with any of the patients given placebo or diazepam.

Blood pressure response in the period during and immediately after administration of the local anesthetic (lidocaine with epinephrine) was not significantly different from placebo responses with either dose of THC or diazepam.

Heart Rate.—Comparison between both dosages of THC, which induced tachycardia in all surgical patients, and response to diazepam and placebo premedicants (fig 2) showed the average peak heart rate increase with 0.044 mg/kg THC to be 69% above preoperative baseline and 36% above placebo peak. The greatest elevation occurred ± 18 minutes after the start of drug injection. Peak heart rate increases after 0.022 mg/kg THC occurred typically at the 15-minute postinjection interval, with 53% above preoperative baseline and 26% above placebo peak. Although heart rate peak time was similar with both doses of THC, the duration of tachycardia differed. Whereas average heart rate had returned to placebo levels 75 minutes after injection of 0.022 mg/kg THC, heart rate after 0.044 mg/kg THC had not returned to placebo levels until after the 100-minute postinjection time.

Local-anesthetic administration in patients premedicated with THC had no significant effect on heart rate during or after the injection process. "Highs" experienced after THC premedication did not coincide with peak heart rates, peak tachycardia occurring typically 12 minutes before peak

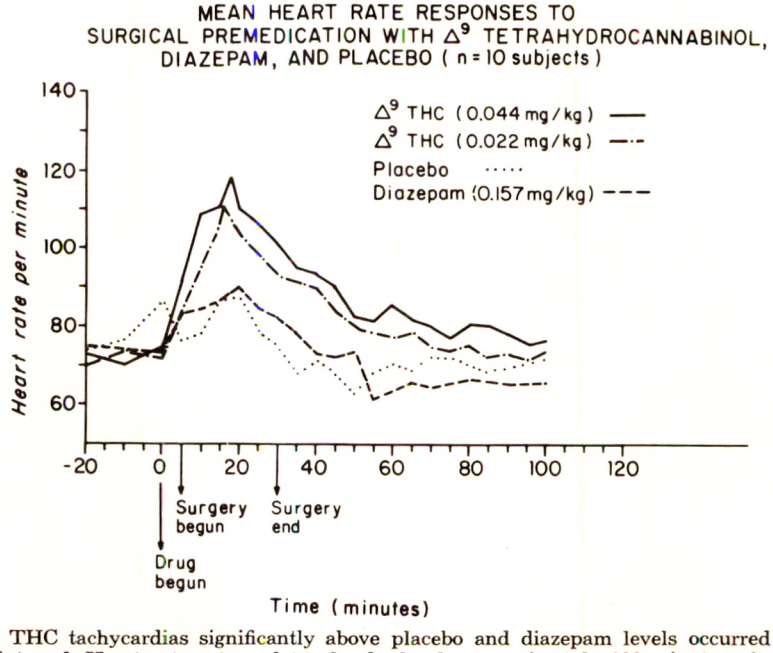


FIG 2. Peak THC tachycardias significantly above placebo and diazepam levels occurred at the 15-18 post-injection interval. Heart rate returned to placebo levels approximately 100 minutes after injection of THC, 0.044 mg/kg.

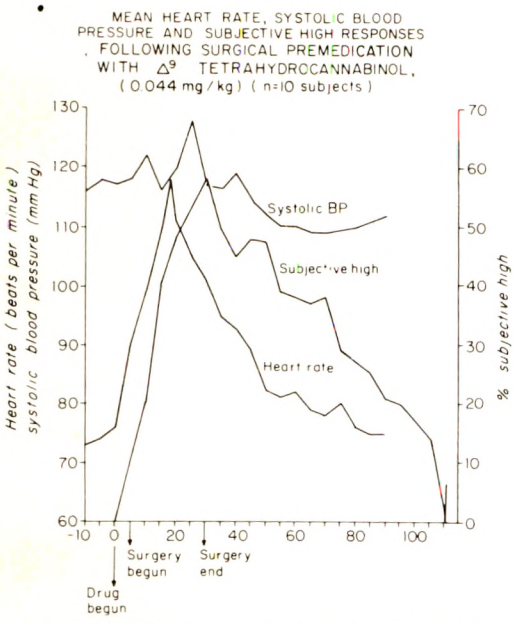


FIG 3. Simultaneous plotting of heart rate, blood pressure and subjective high responses to THC during surgery showed that peak tachycardia preceded both the peak hypertensive and subjective high effect, and that the heart rate and blood pressures returned to placebo baselines an average of 30 minutes before subjective high was reported as normal.

"highs." Heart rates also returned to placebo levels an average of 30 minutes before subjects reported a normal psychic state (fig 3).

ECG Responses.—There was a dose-related shortening of P-R interval greater than 33% in all subjects given THC (table 1). T-wave amplitude reduction of greater than 33% during peak drug effect was observed in 70% of subjects after the smaller doses of THC and in 60% of subjects after the larger THC dose, as compared to a 30% depression with diazepam and 10% depression with placebo. ECG changes in THC-premedicated patients were the same with local anesthetic injection as with placebo.

Arrhythmias, interpreted as functional premature ventricular contractions (PVCs), were observed in 11/40 clinical trials during baseline preoperative recording and in 2/10 subjects during intraoperative trial with placebo premedication. After injection of 0.022 mg/kg THC, arrhythmias seen preoperatively in 2 subjects increased slightly in frequency intraoperatively, and PVCs were observed in 2 other subjects who had not displayed arrhythmias during preoperative baseline recording. After injecting the larger dose of THC, arrhythmias observed in a single subject during baseline preoperative recording disappeared for an hour after drug administration and intraoperative recording (fig 4). No other instances of arrhythmia were observed after giving the larger dose of THC.

Surgical and Nonsurgical THC Groups Compared.—A significant difference ($p<0.05$) was seen in peak heart rate between oral surgery patients and nonsurgerized controls given comparable doses of THC (table 2), but no other significant cardiovascular differences were observed between these 2 groups.

Correlated Subjective Psychologic Effects.—STAI anxiety scores were significantly elevated ($p<0.05$) in THC-medicated surgery patients when compared with placebo or diazepam or with nonsurgerized THC

TABLE 1
ECG Responses to Surgical Premedication with Δ9-THC, Diazepam, and Placebo (n = 40)

	P-R*	T wave†	Arrhythmia	
Placebo	10%	10%	Preoperative	20%
			Intraoperative	20%
Diazepam	10%	30%	Preoperative	30%
			Intraoperative	10%
THC (0.022 mg/kg)	60%	70%	Preoperative	20%
			Intraoperative	40%
THC (0.044 mg/kg)	70%	60%	Preoperative	10%
			Intraoperative	0

*Shortening P-R interval greater than 33%.
†Depression of T wave greater than 33%.

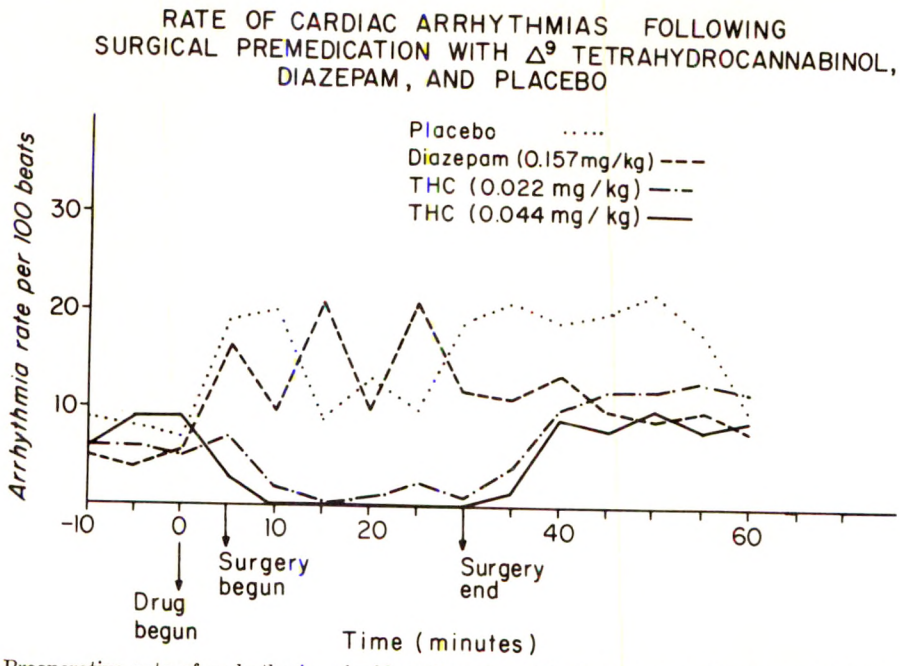


FIG 4. Preoperative rate of arrhythmias significantly reduced following premedication with THC when compared to diazepam and placebo.

TABLE 2
Comparison of Mean Cardiovascular Responses to 0.044 mg/kg IV Δ⁹-THC in Surgical and in Nonsurgical Subjects

	Surgical patients (N = 10) (± SE)		Nonsurgical subjects (N = 5) (± SE)	
Heart rate	Rate	% change baseline	Rate	% change baseline
Baseline	71.7 ±4.5	—	70.8 ±4.2	—
Drug given (5 min)	96.8 ±5.1	35.0*	80.6 ±2.8	13.8*
Peak effect	117.8 ±7.1	64.3*	102.0 ±4.6	44.1*
Trial end (90 min)	80.9 ±7.0	12.8†	73.0 ±2.5	3.1†
Blood pressure	Systolic/diastolic pressure S/D	% change baseline	Systolic/diastolic pressure S/D	% change baseline
Baseline	117.6/76.2 ±5.74/±4.6	—	128.6/68.8 ±4.52/±4.2	—
Drug given	117.2/72.0 ±5.3/±3.8	−0.3/−5.5†	131.8/70.8 ±5.3/±3.5	2.4/2.9†
Peak effect	122.9/68.1 ±7.3/±4.1	4.5/−10.6†	142/73.2 ±12.5/±4.1	10.4/6.4†
Trial end (90 min)	111.8/69.6 ±4.2/±3.6	−4.9/−8.6*	133.8/68 ±7.0/±6.4	4.0/−1.2*

*$p < 0.05$ mean differences in % change from baseline, surgical compared with nonsurgical groups.
†Nonsignificant; differences in % change from baseline, surgical compared with nonsurgical groups.

subjects. Dysphoria, as measured by SDEQ analysis, and "low" moods predominated at the periods of syncopal hypotension after THC.

STUDY 2: METHODS

This retrospective study included 10 consecutive patients, 7 women and 3 men (ages 21 to 30, mean 25 ± 3.1) undergoing outpatient general anesthesia for routine removal of from 2 to 4 third molars in one clinical procedure. Each patient was healthy and free of cardiovascular or respiratory abnormalities and gave informed consent.

At each clinical trial, patients were seated in the operating chair in an approximately 30° upright position with legs parallel to the floor. A venous catheter was inserted in the forearm. Physiologic monitoring consisted of continuous ECG, heart rate, indirect blood pressure, and respiratory rate, by a technic similar to that described for study 1. In addition, serial blood-gas measurements (IL* Blood Gas Analyzer) were made through radial-artery puncture, preoperatively and at selected intervals during operation.

After baseline blood pressure, ECG, heart rate, respiratory rate, and blood gases had been recorded, all 10 patients received the same form of general anesthetic management. First, 0.4 mg of atropine sulfate was administered IV, followed by 0.1 mg of fentanyl. Ten to 15 mg of diazepam was then infused over a 6 to 8-minute period to an endpoint of hypnosis with Verrill's sign (lid lag over pupils). After adequate sedation, N_2O-O_2 (70:30) was administered through a McKesson nasal inhaler by a McKesson Analor® gas machine. After 15 to 30 seconds, 1% sodium methohexital was given at a rate of 20 mg/30 sec until voice contact with the patient was lost.

Following induction, respirations were gently assisted with nasal insufflation, and additional increments of methohexital were infused as needed. Tooth extraction then proceeded according to standard technic, including mouth gauze packing and the PRN administration of local anesthetic blocks. The total usual dose of local anesthetic ranged from 4 to 6 ml of 2% lidocaine (80 to 120 mg) with 40 to 60 mcg of 1:100,000 epinephrine.

Surgical anesthesia ranged from 25 to 45 minutes in duration. No major complications were encountered. Following awakening, patients were monitored for a minimum of 1 hour before discharge.

STUDY 2: RESULTS

Of the 10 patients studied, 5 admitted to having smoked marijuana within 72 hours

*Instrumentation Laboratories.

TABLE 3
Comparison of Mean Cardiovascular Responses to Outpatient General Anesthesia in Marijuana Smokers and in Nonsmokers (N = 10 subjects)

	Blood pressure	Heart rate	Blood gas	
			P_{O_2}	P_{CO_2}
Preoperative baseline				
Smokers	101.6/68.2	83.0	90.0	35.2
Nonsmokers	106.0/66.4	74.8	90.6	36.0
Postinduction				
Smokers	104.8/66.0	104.0	97.6	39.0
Nonsmokers	106.3/68.1	90.3	98.1	44.0
Peak anesthetic				
Smokers	102.0/64.8	98.6	160.2	40.2
Nonsmokers	105.6/65.2	93.6	158.4	40.4
Peak postanesthetic				
Smokers	115.2/89.6	136.8*		
Nonsmokers	116.0/91.2	104.6*		

*$p < 0.05$ mean differences smokers compared with nonsmokers.

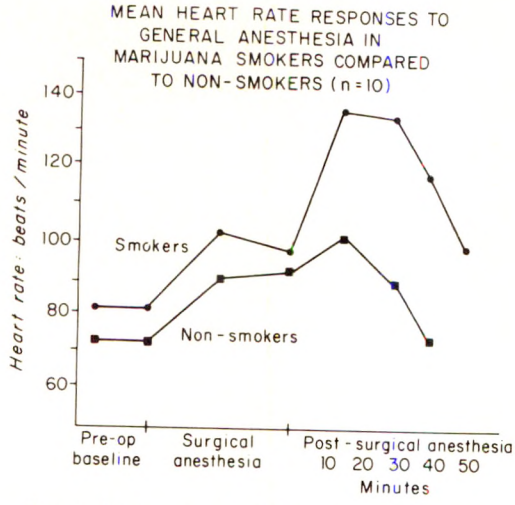


FIG 5. Tachycardia following general anesthesia was markedly elevated and lengthened in marijuana smokers as compared to non-smokers.

of operation. A comparison of cardiovascular responses between marijuana-smoker and nonsmoker groups revealed similar preoperative baselines of blood pressure, heart rate, ECG, and blood gases (table 3). In addition, blood pressure responses and blood gases were found similar and within expected limits for both groups throughout the duration of anesthesia and the postoperative period.

A major difference between the 2 groups was observed, however, in heart rate response during the postanesthetic interval (fig 5). In the marijuana group, a peak tachycardia averaging 64.8% above baseline occurred, which did not return to baseline levels until an average of 38 minutes after the end of anesthesia. In the nonsmoker group, postoperative heart rate peaked at 39% above baseline at the 7-minute mark after anesthesia and returned to baseline levels by the 19-minute mark after anesthesia.

There were no significant differences between smoker and nonsmoker groups for total required methohexital (193 versus 194 mg). Nor were there differences between mean "sleep time" induced by these concentrations (32.4 versus 31.8 min) or in recovery rate.

DISCUSSION

In the current studies, which involved healthy young adults, there was no significant deterioration in cardiovascular functions. However, certain changes were observed that might hold significance for other patient populations.

Transient syncopal hypotension followed THC premedication. (Psychologic measures during these periods demonstrated above-average levels of dysphoria and anxiety.) These patients did not demonstrate syncope when premedicated with placebo or diazepam. Orthostatic hypotension and presyncopal responses to table tilt have been described as common with THC.[31,32] Controlled animal experiments have shown that stress exaggerates an already elevated sympathoadrenal response to parenteral cannabinols, manifest as marked elevations in serum dopamine hydroxylase levels.[25]

Beaconsfield first warned that under stressful or emergency conditions, the vasomotor reflex mechanisms may be significantly impaired in marijuana-pretreated subjects.[14,33] He demonstrated that peripheral blood flow increases concomitantly with pulse rates following cannabinol administration, and that peripheral flow adjustments to mild psychogenic stress (mental arithmetic and ice placed on a limb) are markedly slowed or absent. Careful cardiovascular monitoring, therefore, is mandatory following THC premedication.

After the initial tendency to syncopal hypotension from THC during operation, the blood-pressure response displayed a biphasic pattern of mild hypertension, which peaked at the 25-minute postinjection interval, followed by a gradual hypotensive trend which reached its peak depression at 55 minutes postinjection. Surgical stimulation probably had a strong influence on blood-pressure response. However, similar arousal-depression patterns have been observed in nonsurgical experiments with cannabinols, and there may be pharmacologic reasons for this pattern:[17] As Δ^9-THC undergoes biotransformation to the more polar form, 11-OH-Δ^9-THC, within 10 to 15 minutes after injection, it has been suggested that Δ^9-THC exerts a generalized CNS and cardiovascular arousal effect, and that 11-OH-Δ^9-THC has a longer-acting depressant effect.[34]

In our study, combining THC premedication with the stress of oral surgery appeared to have a synergistic effect on heart rate, since subjects who had received 0.044 mg/kg of THC before operation reached peak heart rates averaging 24.1% higher than the peaks for the nonsurgerized controls. These observations are consistent with current theories

of the mechanism of THC cardiovascular action. Studies have suggested that vagolytic action by the cannabinols is unlikely because cannabinol tachycardia is inducible even in atropinized patients.[14] Most evidence points to a CNS-activated sympathoadrenal response to cannabinol. Beta-adrenergic receptors appear to be the final common pathway for this response, since propranolol, a beta blocker, reduces the effects of cannabinol.[35]

Even though THC tachycardia appeared to be heightened by the stress of operation in this study, it is of interest that the initiation and duration of heart rate changes appeared to precede psychic effects. Onset of heart rate elevation consistently preceded the onset of "highs" by a few minutes, and the peaks of heart rate and subjective "high," as well as the duration curves, were generally out of phase by a matter of many seconds to a few minutes. This finding is consistent with those of Low's group,[13] who observed that subjective THC effects may persist even though heart rate has returned to normal.

It may be speculated that the inevitable THC tachycardia acts as a partial trigger for the psychic effect of cannabinols, and that the surgically stressed patient reacts to tachycardia in a manner different from the nonstressed THC subject. Whereas the nonstressed subject interprets THC tachycardia as an expected and nonthreatening aspect of his drug experience, the stressed patient considers it a signal that is part of an overall harmful situation (the operation) which is out of his control. This activates the hypothalamo-pituitary complex and eventually a classic sympathoadrenal stress response, which then potentiates the preexisting THC tachycardia.

In pursuing one of the goals of the current study, the detection of significant drug interactions between cannabinols and a local anesthetic agent, it was observed that usual surgical levels of 2% lidocaine and 1:100,000 epinephrine had no measurable effect on any cardiovascular parameter. Beaconsfield[33] has shown that THC potentiates the pressor effects of IV epinephrine in humans, while laboratory studies[32,36] have shown elevation of circulating epinephrine for periods of 6 hours following THC administration. It would appear, however, that the doses of lidocaine and epinephrine used in our studies with surgery patients and with routine anesthetic block were insufficient to interact significantly with cannabinol premedication.

An apparent drug interaction was observed, however, in study 2 of this investigation, where a prolonged postoperative tachycardia was observed in a series of patients who had smoked marijuana within 72 hours before undergoing outpatient general anesthesia. Not only is this a potentially dangerous problem, but when the etiology of the tachycardia is not appreciated, errors in medical management may occur.

Previous studies[14] have demonstrated synergistic cardiovascular effects between cannabinols and vagolytic agents. This suggests that atropine, used in the current anesthetic technic, was the drug most likely to have interacted with the previously smoked cannabinol.

Potential drug interactions occurring many hours, or even days, after marijuana smoking appear quite possible, in light of the known distribution, catabolism, and excretion patterns of the cannabinols. Plasma levels of $\triangle^9$-THC decrease rapidly after injection, probably because of a great affinity for fat stores.[37] THC may also be stored in significant quantities in the enterohepatic tissues and be secreted along with bile in response to food ingestion.[9] Although this appears to be the primary means of cannabinol excretion, with 70 to 80% eliminated in the feces and 20 to 30% in the urine, the enterohepatic secretion, with subsequent plasma resorption from the gut, may also account for the frequently observed maintenance of sustained and episodic THC plasma levels.[38]

The plasma half-life of $\triangle^9$-THC is 36 hours; that of the active liver metabolite, 11-OH-$\triangle^9$-THC, is 40 hours. The release of active THC compounds has been shown to continue for 8 days after a single human dose.[7,34] Therefore, 20 to 35% of active cannabinols may remain in the tissues for longer than 72 hours after a single administration. This time course is quite compatible with the sequence of drug interactions suggested by our study 2.

An acute dose-related antiarrhythmic effect was observed during oral surgery with THC premedication. The smaller doses of $\triangle^9$-THC were associated with intraoperative PVC activity at levels similar to those of placebo, whereas the larger doses were correlated with the disappearance of arrhythmias after injection. Although some

authors[17,20] report possible induction of arrhythmias by cannabinols, other observers[21,39] have shown possible antiarrhythmic effects. In our study, arrhythmias were of the benign variety, consisting mainly of transitory ectopic foci. It would be unwise to assume that a similar therapeutic effect would have occurred in a group of patients with chronic cardiopathy.

We conclude that Δ^9-THC has no particular advantage over diazepam or placebo as a premedicant; although potentially therapeutic antiarrhythmic effects were seen, THC appeared to compromise to some degree the surgical patient's adaptivity to stress and to interact undesirably with other anesthetic medications.

REFERENCES

1. Marijuana and Health. Washington, DC, Third Annual Report to Congress, DHEW Pub # (ADM) 74-50, 1974

2. Parker JS, Dubas TC: Automatic determination of the pain threshold to electroshock and the effects of Δ^9-THC. Int J Clin Pharmacol 7:75-81, 1973

3. Jones RT: Marijuana-induced "high": influence of expectation, setting and previous drug experience. Pharmacol Rev 23:359-369, 1971

4. Klonoff H, Low M, Marcus A: Neuropsychological effects of marijuana. Can Med Assoc J 108:150-165, 1973

5. Nahas GG: Toxicology and pharmacology of *Cannabis sativa* with special reference to Δ^9-THC. Bull Narc 24:11-29, 1972

6. Hill SY, Goodwin DW, Schwin R, Powell B: Marijuana: CNS depressant or excitant? Am J Psychiatry 131:313-315, 1974

7. Lemberger L, Weiss JL, Watanabe AM, et al: Delta-9-tetrahydrocannabinol. Temporal correlation of the psychologic effects and blood levels after various routes of administration. N Engl J Med 286:685-688, 1972

8. Klapper JA, McCollach MA, Sidell FR: The effect of personality on reactivity to 1,2-dimethylheptyl tetrahydrocannabinol. Arch Gen Psychiatry 26:483-485, 1972

9. Mills L, Brawley P: The psychopharmacology of "Cannabis sativa": a review. Agents Actions 2: 201-215, 1972

10. Carlin AS, Bakkar CB, Halpern L, et al: Social facilitation of marijuana intoxication: impact of social set. J Abnorm Psychol 80:132-140, 1972

11. Ablon SL, Goodwin FK: High frequency of dysphoric reactions to tetrahydrocannabinol among depressed patients. Am J Psychiatry 132:448-453, 1974

12. Bilash IS, Arnold M, Zell C: Marijuana and suggestibility. Can Psychiatr Assoc J 17:327-329, 1972

13. Low MD, Klonoff J, Marcus A: The neurophysiological basis of the marijuana experience. Can Med Assoc J 108:157-165, 1973

14. Beaconsfield P, Ginsburg J, Rainsbury R: Marijuana smoking: cardiovascular effects in man and possible mechanisms. N Engl J Med 287:209-212, 1972

15. Renault PF, Schuster CR, Heinrich R, et al: Marijuana: standardized smoke administration and dose effect curves on heart rate in humans. Science 174:589-591, 1971

16. Williams RB, Ng LK, Lamprecht F, et al: Δ^9Tetrahydrocannabinol: a hypotensive effect in rats. Psychopharmacology 28:269-274, 1973

17. Johnson S, Domino EF: Some cardiovascular effects of marijuana smoking in normal volunteers. Clin Pharmacol Ther 12:762-768, 1971

18. Aronow WS, Cassidy J: Effect of marijuana and placebo-marijuana smoking on angina pectoris. N Engl J Med 291:65-67, 1974

19. Rubin V, Comitas L: Effects of Cannabis in another culture. Scotch Plains, NJ, Mouton/McFarland Publications, 1975

20. Kochar MS, Hosko MJ: Electrocardiographic effects of marijuana. JAMA 225:25-27, 1973

21. Roth WT, Tinklenberg JR, Kopell BS, et al: Continuous electrocardiographic monitoring during marijuana intoxication. Clin Pharmacol Ther 14: 533-540, 1973

22. Driscoll EJ, Smilack ZH, Lightbody PM, et al: Sedation with intravenous diazepam. J Oral Surg 30:332-343, 1972

23. Sofia RD, Knobloch LC: The effect of Δ^9-tetrahydrocannabinol pretreatment on ketamine thiopental or CT-1341-induced loss of righting reflex in mice. Arch Int Pharmacodyn Ther 207:270-281, 1974

24. Siemens AJ, Kalant H, Khanna JM, et al: Effect of cannabis on pentobarbital-induced sleeping time and pentobarbital metabolism in the rat. Biochem Pharmacol 23:447-488, 1974

25. Ng LK, Lamprecht F, Williams RB, et al: Δ^9 tetrahydrocannabinol and ethanol: differential effects on sympathetic activity in differing environmental settings. Science 180:1368-1369, 1973

26. Zalcman S, Liskow B, Cadoret R, et al: Marijuana and amphetamine: the question of interaction. Am J Psychiatry 130:707-708, 1973

27. Spielberger CK, Gorsuch RL, Lushene RE: State-Trait Anxiety Inventory. Palo Alto, Consulting Psychologists Press, 1970

28. Waskow IE, Olsson JE, Salzman C, et al: Psychological effects of tetrahydrocannabinol. Arch Gen Psychiatry 22:97-105, 1970

29. Perez-Reyes M, Timmons MC, Lopton MA, et al: Intravenous injection in man of Δ^9-tetrahydrocannabinol and 11-OH-Δ^9-tetrahydrocannabinol. Science 117:633-635, 1972

30. Gregg JM, Small EW, Moore R, et al: Emotional responses to intravenous Δ^9-tetrahydro-

cannabinol during oral surgery. J Oral Surg (in press)

31. Hardman HF, Domino EF, Seevers MG: General pharmacological actions of some synthetic tetrahydrocannabinol derivatives. Pharmacol Rev 23:295-316, 1971

32. Weiss JL, Watanabe AM, Lemberger L, et al: Cardiovascular effects of delta-9-tetrahydrocannabinol in man. Clin Pharmacol Ther 13:671-684, 1972

33. Beaconsfield P: Some cardiovascular effects of cannabis. Am Heart J 87:143-146, 1974

34. Lemberger L, Axelrod J, Kopin IJ: Metabolism and disposition of $\triangle^9$-tetrahydrocannabinol in man. Pharmacol Rev 23:371-380, 1971

35. Drew WG, Kiplinger GF, Miller LL, et al: Effects of propranolol on marijuana-induced cognitive dysfunctioning. Clin Pharmacol Ther 13:526-533, 1972

36. Hollister LE, Moore F, Kanter S, et al: $\triangle^9$-tetrahydrocannabinol, Synhexyl and marijuana extract administered orally in man: catecholamine excretion, plasma cortisol levels and platelet serotonin content. Psychopharmacologia 17:354-360, 1970

37. Kreuz DS, Axelrod J: Delta-9-tetrahydrocannabinol: localization in body fat. Science 179: 391-392, 1973

38. Lemberger L, Martz R, Rodda B, et al: Comparative pharmacology of $\triangle^9$-tetrahydrocannabinol and its metabolite, 11-OH-$\triangle^9$-tetrahydrocannabinol. J Clin Invest 52:2411-2417, 1973

39. Schaefer JF, Loetzer R, Sofia RD: Effect of $\triangle^1$-tetrahydrocannabinol and propranolol on ouabain induced arrhythmias. Arch Int Pharmacodyn Ther 205:5-10, 1973

TEMPERATURE AND d-TUBOCURARINE The influence of temperature (28-41C) on d-tubocurarine (dTc) neuromuscular blockade and antagonism with neostigmine was studied in anesthetized cats. dTc infusion rate required to maintain 90 per cent twitch depression was directly related to temperature. Although the mechanism is not known, reduced renal and biliary excretion of dTc, may account for the decreased dTc needs during hypothermia. Hypothermia did not affect the magnitude but prolonged the onset and then duration of dTc antagonism by neostigmine. Since hypothermia reduces skeletal muscle blood flow the delayed uptake and elimination of neostigmine should not be unexpected. *(Miller RD, Van Nyhuis LS, Eger EI: The effect of temperature on a d-tubocurarine neuromuscular blockade and its antagonism by neostigmine. J Pharm Exp Ther 195:237-241, 1975)*

Management of a Parturient with Cardiac Valve Prosthesis

DEMIR M. SAKA, MD*
GERTIE F. MARX, MD†
Bronx, New York‡

The parturient with a cardiac valve prosthesis presents a twofold problem of management: (1) that of a rising cardiac workload in the presence of serious heart disease, and (2) that of chronic anticoagulant therapy. Pain relief, a shortened 2nd stage of labor, and avoidance of bearing-down efforts reduce stress. Vaginal delivery is preferred to cesarean section, and segmental lumbar extradural block is the optimal anesthetic method. Oxytocics must be used with caution and heparin is preferred to long-acting oral anticoagulants.

A 24-YEAR-OLD hemiparetic woman, a known rheumatic cardiac patient with a mitral valve replacement, came to our emergency room with a vague history of amenorrhea and complaints of low back pain, abdominal discomfort, and breast fullness. She was 4 months pregnant and desired continuation of the pregnancy. She was admitted to our prenatal unit for continued care until delivery.

At 5 years of age, she had had rheumatic fever, but maintained a normal life until the age of 19, when she had a cerebrovascular accident. A diagnosis of mitral stenosis was made and she was placed on anticoagulant therapy. Cardiac catheterization 1 year later revealed the presence of mitral and aortic insufficiency in addition to mitral stenosis, and mitral commissurotomy and valvuloplasty were performed with good result.

Ten months later, she injected heroin with an unclean syringe and developed *Staphylococcus aureus septicemia*, leading to acute bacterial endocarditis which primarily affected the mitral valve. Emergency mitral valve replacement was undertaken. For the 4 years prior to the present admission, she was on maintenance doses of digoxin, furosemide, and hydroxycoumarin, and had successfully withdrawn from narcotic addiction.

Physical examination revealed a chronically ill patient with left hemiparesis, walking slowly with the aid of a cane. She developed dyspnea on minimal exertion and was classified as an AHA class III heart patient. Blood pressure was 120/70 torr, heart rate 80 to 90 and grossly irregular. Auscultatory findings were commensurate with the presence of a mitral prosthetic valve and aortic insufficiency. An ECG showed atrial fibrillation with occasional premature ventricular contractions.

Throughout her stay in the hospital, the patient was on a low-sodium diet and was taking digoxin, diuretics, iron sulfate, and anticoagulants (sodium warfarin until the 36th week of gestation, heparin 5000 units every 6 hours thereafter).

The pregnancy progressed satisfactorily. One episode of congestive heart failure during the 2nd trimester was treated successfully with increased doses of digoxin and furosemide. At 39 weeks of gestation, the patient was considered ready for delivery

*Instructor in Anesthesiology.
†Professor of Anesthesiology.
‡Department of Anesthesiology, Albert Einstein College of Medicine, Bronx, New York 10461.

Paper received: 7/21/75
Accepted for publication: 8/8/75

(the cervix was favorable for induction and the fetus was mature). Accordingly, heparin was discontinued, kanamycin and penicillin administered intramuscularly, and membranes ruptured artificially. Regular contractions began 3 hours later.

A slow IV infusion of 5% dextrose in 1/3 NaCl (50 ml/hr) was started, and blood obtained for cross-match, clotting time, and prothrombin time determination. Clotting time (Lee-White) was 26 minutes and prothrombin time 21 seconds (control 11.5). Protamine sulfate (total of 25 mg) was given in increments until coagulation values became and remained normal.

As soon as cervical dilation permitted, internal monitoring of uterine pressure and fetal ECG was begun. At 5 cm dilation, a continuous lumbar extradural block was initiated using a 17-gauge thin-walled Tuohy needle and a Teflon-styleted catheter, which was threaded cephalad. The patient's right hip was elevated by a foam-rubber wedge (to prevent aortocaval compression), and O_2 was administered continuously by face shield. For pain relief of the 1st stage of labor, a segmental block from T9 through L1-2 was achieved with 2% 2-chloroprocaine, using a total of 360 mg over a 2¼-hour period. Chloroprocaine (3%, 6 ml) injected in the sitting position provided perineal analgesia.

A normal healthy infant (Apgar scores 8 to 10) weighing 3050 gm, was delivered by low-mid forceps over a mediolateral episiotomy after 45 minutes of 2nd-stage labor. Synthetic oxytocin (10 units) was added to 500 ml of IV fluid after expulsion of the placenta. Blood loss was less than 250 ml, and vital signs remained stable (BP 120/70 to 110/60, heart rate 96 to 108 during labor, 88 postpartum). Following repair of the episiotomy, another 6 ml of 3% chloroprocaine was administered, resulting in a sensory level of T8 and producing analgesia for bilateral tubal ligation (through a 5-cm subumbilical incision, with blood loss of 20 ml).

Lead II of the ECG was monitored throughout the course of extradural block and showed unchanging atrial fibrillation. There appeared to be no danger of postpartum cardiac failure, and the extradural catheter was removed at the end of the operative procedure. Heparinization was restarted 24 hours later, and the mother ambulated shortly thereafter. Both mother and infant had an uneventful course.

DISCUSSION

The pregnant woman with cardiac valve prosthesis presents a twofold problem of management: (1) that of a rising cardiac workload in the presence of serious heart disease, and (2) that of chronic anticoagulant therapy.[1] Cardiac output and left ventricular work, which rise steadily during gestation, are further increased during each effective uterine contraction.[2] However, their cumulative increases can be significantly reduced by adequate pain relief, a shortened 2nd stage of labor, and avoidance of bearing-down efforts.[3,4]

It has been stated that the ideal delivery for the parturient with acquired heart disease is "one which is accomplished using simple outlet forceps under some form of regional anesthesia," preferably continuous extradural block.[4] Segmental lumbar extradural analgesia is optimal because pain relief is specific while the disadvantages of more extensive blockade are prevented; yet the technic can be employed to reduce venous return to the heart, should cardiac failure with pulmonary edema suddenly occur. We chose chloroprocaine as the local anesthetic because of the versatility and safety offered by its short duration of action.

It is evident that hypotension should be avoided. However, blood pressure ought not decline significantly or at all, if a segmental block is executed judiciously and compression of the inferior vena cava circumvented. If, nevertheless, vasopressor treatment becomes necessary, the choice of drug depends upon the cardiac disease. Although ephedrine is preferred from the viewpoint of the fetus, it is contraindicated whenever increases in cardiac output and/or rate are harmful to the mother. In such situations, a dilute solution of phenylephrine or norepinephrine is recommended.

Oxygen inhalation by face shield or nasal cannula is beneficial in view of the increased O_2 consumption associated with labor, and administration of broad-spectrum antibiotics is advocated as prophylaxis against the development of bacterial endocarditis at parturition. Oxytocics must be used with caution. Ergonovine-type drugs are vasoconstrictors which raise venous and arterial pressures, whereas the synthetic oxytocins are vasodilators capable of producing marked hypotension. Only a dilute solution of a synthetic oxytocin should be administered to a cardiac patient.

Heart disease, per se, is no indication for

cesarean section. Despite the repetitive hemodynamic alterations caused by labor, vaginal delivery offers advantages to both mother and neonate. The mother benefits from lesser blood loss, lesser danger of wound infection or dehiscence, lesser hazard of thrombophlebitis, and lesser incidence of bleeding following reheparinization; the infant, from more physiologic preparation for extrauterine life.

Anticoagulation constitutes a special problem during pregnancy. The long-acting oral anticoagulants, consisting of small molecules, traverse the placenta freely, with possible teratogenicity and hemorrhagic potential in placenta and fetus.[1] In addition, reversal of their effect is slow. They should not be used during the 1st trimester or near term. Instead, heparin, which does not pass the placenta and can be reversed easily, should be employed in the beginning and in the last 4 to 6 weeks of gestation. At the onset of labor, heparin should be discontinued and reinstituted 24 hours after delivery. Within 5 to 7 days postpartum, oral anticoagulants can again replace heparin.

Because of a recent case report of extradural hematoma formation in a patient with occlusion of the popliteal artery, who was started on heparin therapy 20 minutes after initiation of a continuous extradural block,[5] we did not reheparinize our patient until 24 hours after removal of the catheter.

The long-standing hemiparesis was not considered a contraindication to extradural analgesia, as it was the result of embolization from mitral stenosis, a disease process eliminated since, and did not represent a neurologic disease with the potential of progression or exacerbation.

REFERENCES

1. Tejani N: Anticoagulant therapy with cardiac valve prosthesis during pregnancy. Obstet Gynecol 42:785-793, 1973

2. Adams JQ, Alexander AM: Alterations in cardiovascular physiology during labor. Obstet Gynecol 12:542-549, 1958

3. Ueland K, Hansen JM: Maternal cardiovascular dynamics. III. Labor and delivery under local and caudal analgesia. Am J Obstet Gynecol 103: 8-18, 1968

4. Bonica JJ, Ueland K: Heart disease, Principles and Practice of Obstetric Analgesia and Anesthesia. Edited by JJ Bonica. Philadelphia, FA Davis Company, 1969, chapter 53, pp 941-977

5. Varkey GP, Brindle GF: Peripheral anaesthesia and anti-coagulant therapy. Can Anaesth Soc J 21:106-109, 1974

CSF AND CEREBRAL ANOXIA Changes in cisternal and lumbar cerebrospinal fluid (CSF) were measured to determine metabolic changes in the central nervous system after profound anoxia. In 12 patients who could not be resuscitated the cisternal CSF pH was more acid and the potassium concentration double that in lumbar CSF. These data suggest that potassium and hydrogen ions leave the brain cells during anoxia and these changes are more accurately reflected by cisternal than lumbar CSF. Marked increases in extracellular fluid potassium may produce vasoconstriction and impair re-establishment of regional cerebral blood flow following ischemia. Cisternal CSF was normal in a group of patients who were successfully resuscitated. *(Kalin EM, Tweed WA, Lee J et al: Cerebrospinal-fluid acid-base and electrolyte changes resulting from cerebral anoxia in man. NEJM 293:1013-1016, 1975)*

A Potential Ignition Source in the Operating Room

EDWARD F. ANDERSON, LCDR, USN (MC)*

Close proximity or point-to-point contact between the posterior aspect of the light in the Castle/Daystar® lighting system and the O_2 supply tubing can result in the development of hypoxia or in an explosion, as described in the following case report.

BECAUSE of the decrease in use of flammable anesthetic gases and vapors, there has been a corresponding decrease in concern as to the possibility of fires and explosions in the operating room.[1] However rare, fires and explosions still occur, as was demonstrated by a recent report of a flash fire after the use of a skin prep spray and electrocautery.[2]

An unusual potential ignition source in the operating room is described in the following case report.

CASE REPORT

The patient was a 64-year-old ASA class II woman having an exploratory laparotomy. General endotracheal anesthesia, using a balanced technic consisting of N_2O-O_2, meperidine, and d-tubocurarine, was administered.

Approximately 2 hours after the incision, the orbiter lights of the Castle/Daystar® Surgical Lighting System were adjusted for better lighting in the operative field. Ten minutes after the above placement, a loud "pop" was heard, followed by a continuous, loud "hiss." The posterior aspect of one lamp was found to be 3.8 cm from the O_2 supply tubing, at a point 15.2 cm from the O_2 outlet in the overhead console above the anesthesiologist. The O_2 tank was turned on, after which the O_2 supply tubing was disconnected from the outlet. A 1-cm-long break (figure) was noted in the O_2 supply tube, with no observable melting of the material. No damage or injury to the patient or operating room personnel occurred, and the operation continued without further incident.

DISCUSSION

Despite the decrease in use of flammable anesthetics, fire and explosions are still a threat. Many items used in the operating room are flammable, including: "gauze pads and sponges, adhesive tape (especially plastic), eye patches, drapes, prepping solutions, and rubber endotracheal tubes."[1] When combined with a source of ignition and increased concentrations of O_2 or N_2O, fires and explosions are possible.

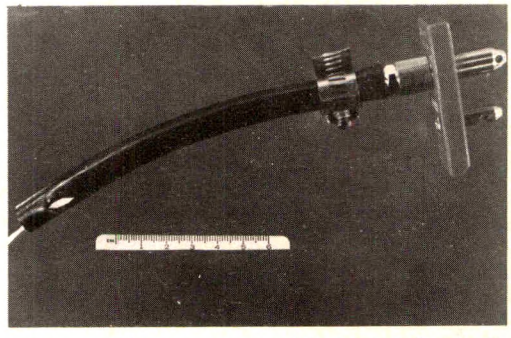


FIGURE. White arrow (at left) shows defect in O_2 supply tubing.

*Staff Anesthesiologist, Assistant Head, Department of Anesthesiology, Naval Regional Medical Center, Great Lakes, Illinois 60088.

The opinions expressed in this paper are those of the author and do not reflect the views of the US Naval Regional Medical Center, Great Lakes, the Bureau of Medicine and Surgery, or the US Navy.

Paper received: 6/25/75
Accepted for publication: 8/4/75

The O_2 supply outlet in the case described above was up beyond the 1.5-m hazardous area,[3] and the supply tubing was conductive; thus both conformed to the standards for the use of inhalation anesthetics.[4] The Castle/Daystar system gives color close to true daylight on the operative field, while transmitting "substantially less heat in the surgical field per foot candle of illumination." The cold mirror reflectors and optical train direct the high-intensity visible light to the field and about 80% of the infrared energy upward through the backs of the reflectors away from the surgical field.[5]

The O_2 tubing was manufactured by the Chemetron Corporation. It was composed of vinyl plastic, had a melting point of approximately 315 C, a bursting pressure of 325 psi, and had been in use for 6 months.

To determine whether the above incident could be reproduced, other tubing was placed in soft, point-to-point contact against the central rear surface of the orbiter light with the O_2 flowing at 2 L/min. Tubing from another machine had a blowout in 55 seconds. Fresh, unused tubing blew in 65 seconds with the light in question and in 67 seconds with another orbiter light.

Increasing the temperature of the O_2 supply tubing progressively weakened the walls until they were no longer capable of supporting the moderate pressure (50 psi) at which the O_2 is supplied. The resulting "blowout" could lead to the development of hypoxia (should the O_2 tanks not be turned on) by allowing the O_2 to escape through the lower resistance hole into the operating room atmosphere. Furthermore, if there were direct contact between the O_2 tubing and the posterior of the lamp or if flammable anesthetics or other combustible substances were present with an elevated temperature, an explosion might have occurred.[6]

ACKNOWLEDGMENT

The author thanks the following for their help in making this article possible: CDR John P. Swope, MC, USN; LCDR Frederick Arnold, MC, USNR; Ms Chlorina Z. Mcallister, HMC Lynn Finch, USN.

REFERENCES

1. Perry LB, Gould AB Jr, Leonard PF: Case History 82: "Nonflammable" fires in the operating room. Anesth & Analg 54:152-154, 1975

2. Plumlee JE: Operating-room flash fire from use of cautery after aerosol spray: a case report. Anesth & Analg 52:202-203, 1973

3. Walter C: Anesthetic explosions: a continuing threat. Anesthesiology 25:505-514, 1964

4. National Fire Protection Association: Standard for the use of inhalation anesthetics. Code 56A, 1972

5. Castle/Daystar Surgical Light (L-900) operators manual, Castle Sybron Corporation, revised September 15, 1970

6. Macintosh R, Mushin WW, Epstein HG: Physics for the Anaesthetist. London, Blackwell Scientific Publications, 1963, p 385

SUPRASTERNAL PALPATION Measurements of tracheal length (inspiratory chest radiographs) in non-intubated infants revealed the tracheal midpoint to be within 0.5 cm of the interclavicular midpoint. With the head in a neutral position, an endotracheal tube with stylet is passed through the glottic opening until the tip is palpated in the suprasternal notch at the level of the clavicles. Thirteen intubations performed with external tracheal palpation were confirmed to be within 1 cm of the interclavicular midpoint while only 3 of 14 tracheal tubes were so placed without external palpation. Auscultation was unreliable as the distal end of the tracheal tube could be 1 cm in either bronchus without changes in breath sounds. Disadvantages of this technique include the need for two people and the use of a stylet. *(Bednerek FJ, Kuhns LR: Endotracheal tube placement in infants determined by suprasternal palpation: A new technique. Peds 56:224-229, 1975)*

In each issue of the Journal an article of particular interest and value to anesthesiologists, which has been published elsewhere, will be presented. Primarily the material will contain fundamental basic information which has been presented by anesthesiologists, physiologists, pharmacologists, and others and, on occasion, by commercial firms. In the last instance, these reprintings are not to be construed as an endorsement of the particular commercial firm or its product by Anesthesia and Analgesia—Current Researches.

Righting the Wrongs of Writing: Copy Editors Speak Out

JACLYN J. ALEXANDER
JUDY WALL

The major part of APGA Press production editor's jobs is copy editing manuscripts before they are set in type. In this article, written at the invitation of the P&G editor, two APGA Press Staff members use specific examples to illustrate the grammatical and stylistic errors that cause problems for them and, if not corrected, for readers. The authors hope that contributors and potential contributors to professional journals will find this article helpful in expressing their ideas clearly when preparing material for publication.

IT'S A typical day in the Press Staff offices.

The managing editor's phone rings.

"APGA Press."

"Jackie? It's Jude. I can't figure out this sentence."

"Okay, read it to me."

"It says, 'It has been thusly observed that students in contiguous areas of growth at various levels, no matter where they are, come to the counselor for help with the presumptuousness of effectiveness of facilitation.' "

"What???"

"Well, I have no idea what these authors are talking about."

"What's the article about?"

"It's about the characteristics of undergraduate students who seek counseling."

"All right, let's take it one step at a time. What does the pronoun *they* refer to? Students? Areas? Levels?"

Jaclyn J. Alexander is Managing Editor of the APGA Press and has been copy and production editor for several of the APGA divisional journals. Judy Wall is Senior Editor on the APGA Press Staff and copy and production editor of the PERSONNEL AND GUIDANCE JOURNAL. The authors express their thanks to Richard Wall for his help in the revising and polishing of the manuscript (despite their advice in this article to have manuscripts critiqued by objective outsiders).

Copyright (1975) American Personnel and Guidance Association. Reprinted with permission.

TEN MINUTES LATER:

"Okay, read it back to me. What have we got?"

"Here it is: 'We have seen that students at all levels of growth come to the counselor for help and expect to receive it.' "

Conversations of this kind take place often around the APGA Press. In this case we were able to figure out what the authors wanted to say and help them say it clearly. We can't always. Sometimes a sentence is so awkward that we don't know what the author is trying to say, and chances are that the reader won't either. We thought it might be helpful to share with P&G readers and potential contributors some of the misuses and poor uses of language we have come across in articles we have edited. By being aware of some of the common writing faults that can lead to misinterpretation, an author can avoid them.

WHY COPY EDITORS?

Copy editors, those mysterious, behind-the-scenes people on the staffs of every book publishing company, magazine, journal, and newspaper, have a major job: to help writers communicate their ideas to readers as clearly and effectively as possible. Essentially this process entails improving readability by correcting grammatical errors and making stylistic changes. Depending on the literary medium they are working in, copy editors' tasks vary. Although our experience has been primarily in journal work, and our examples are drawn from this medium, what we have to say is applicable to all types of writing.

A professional journal article is expository in nature. The author's purpose is to present a point of view, an idea, a finding, or a program to a readership of professional colleagues. In other words, the article is designed to inform. To communicate. To talk to people. When the writing technique or style interferes with or detracts from the ideas, the purpose is defeated.

This is where we come in. On the following pages are some examples of the kinds of changes we make in manuscripts to clarify meaning and improve readability.

RIGHTING THE WRONGS OF WRITING

There are two types of problems that give copy editors headaches. One is that of grammar and syntax—a misplaced comma, an incorrectly used conjunction, a pronoun with an unclear referent. The other, harder to define, concerns style and readability. We'll take the second one first.

STYLE AND READABILITY

Some years ago, a newscaster reported on a national news station, "He shot his girlfriend in the Bronx." If you've ever been shot in the Bronx, you know how painful that can be.

Okay. Everybody knew what he meant; the point is that it sounded a little silly. Style is not what you say but how you say it. Remember, the purpose of professional journal material is to communicate. Anything—a paragraph, a sentence, a phrase, or even a word—that doesn't work smoothly to that end doesn't belong there. There are several ways that style can interfere with communication.

Short and Sweet Says It Best.—Writing principle number one, and also principles number two, three, and four, is *economy of expression.* No matter what the medium, the straightforward, declarative sentence is the most direct way of communicating. You can't beat it. Unnecessarily long and involved sentences only confuse readers. Such sentences crop up when an author tries to cram too many ideas into one sentence. When a sentence has too many clauses, too many "whiches," the reader tends to try to sort out the sentence instead of paying attention to what the author is saying. Sentences needn't be choppy, but they shouldn't be so complicated that the reader must read them two or three times to understand the meaning.

The following is a good example. "The client who has been referred within himself or herself predetermines and verbalizes to the counselor to whom he or she has been referred about what his or her counterproductive behaviors are or are not, makes decisions regarding which of such behaviors she or he can commit himself or herself to work on, with the counselor, of course, and the counselor facilitates the setting of aforementioned goals related to the replacement of such with more positive behavioral performances, or goals related to the acquisition of such which had not previously been within the viable parameters of the client's activity-oriented repertoire." Whew. Authors may know what they mean when they write sentences such as that one, but, being more involved with their ideas than with their words, they don't express the meaning succinctly and clearly.

Where language and diction (word choice) are concerned, economy of expression is again the key. Unusual word usages are detrimental to communication when they draw attention to themselves and away from the writer's ideas. When a short, simple, common word will do, use it in place of a long, unusual one. Why send readers scurrying to their dictionaries to look up *perdure* and *extirpate* when *last* and *destroy* will convey the meaning? The impression this gives is that the author is trying to impress readers with an extensive vocabulary. They may indeed be impressed. They may also miss the author's meaning. Using simple words is not necessarily patronizing. Rather, it makes for clear, precise, direct communication.

Another diction fault may have the opposite effect: It may put readers to sleep. We're talking about the tendency to repeat the same word or phrase over and over again. Using interesting synonyms makes uninteresting writing more interesting for interested readers. Oops. What we meant to say was that the use of interesting synonyms makes dull writing come alive for attentive readers.

Writing in Action, or, Action in Writing. A problem on the more technical side is the use of the passive voice. Here's a quick grammar lesson, before you go hunting for your fifteen-year-old's grammar text in order to get through this paragraph. *I taught the class* has an active verb. *The class was taught by me* has a passive verb. Both sentences are grammatically correct, and in both the meaning is clear. The difference is in the emphasis. In the second case the grammatical subject of the sentence is not the person who is doing the acting (*me*) but the thing that is being acted on (*the class*).

We've seen many articles full of good ideas that might have been interesting but weren't because sentence after sentence had passive verbs. This kind of writing is boring and dry because it is literally passive; there is no action taking place, no movement to keep the reader interested. Unfortunately, this is the least of the difficulties. Often a sentence written in the passive voice is at best ridiculous, at worst incomprehensible. One author wrote, *Courses are taught by the counselors in mental institutions.* The copy editor changed it to read *The counselors teach courses to patients who are in mental institutions,* lest young counselor trainees get the wrong impression about what will happen to them after they get out of school. *Counselors and students plan a curriculum together, and a student portfolio is maintained.* Obviously, it is not clear who is keeping the portfolio. Are counselors keeping tabs on the students? Are students recording their own progress? Or is a third party keeping this log? This is a case in which the active voice is imperative for clarification.

In other words, don't say *it can be seen that;* say *we can see that.* Don't say *it is hoped by this author that;* say *I hope that.* Don't say *it has been shown by researchers that;* say *researchers have shown that.* In your reading, watch for passive construction and see how it detracts from the impact of a sentence. Watch for it also in your writing, and change it!

The Medium, the Message, the Method. A more general style issue authors should be concerned with is the appropriateness of language. Metaphors, analogies, images, and poetic phrases are often inappropriate in expository writing because they are distracting. As with unusual word usages, these figures of speech draw attention to themselves. We have come across sentences such as these in journal manuscripts: *In order to relate to clients, the counselor must empathically wear his heart on his sleeve.* Sounds pretty messy. *The book provided a veritable treasure chest of pearls of wisdom for those who read it.* A real gem. *Driving down the narrow and winding highway of life, we counselors have a panoramic view of the lonely, alienated counselee-hitchhikers who beckon to us to stop and help them. Will we heed the call of their supplicating thumbs?* Good grief.

Imagery and poetic language work only when they are fresh, interesting, and to the point. Words and phrases that are trite don't work in any context. Only the most skillful writers can combine expository and creative writing without causing a jarring effect on the reader.

We can't leave this topic without saying a word about professional jargon. In many cases counseling terminology has specific meaning, and people in the field understand it. But many times a word or phrase is

"A professional journal article is designed to inform. To communicate. To talk to people. When the writing interferes with the ideas, the purpose is defeated."

overblown; the writer could substitute a simple word or phrase without sacrificing the meaning. In speaking of jargon, Edwin Newman, in *Strictly Speaking: Will America Be the Death of English?*, says, "A large part of social scientific practice consists of taking clear ideas and making them opaque" (1974, p. 146). He goes on to say,

> For a social scientist to make obscure what he considers to be unnecessarily clear calls not so much for an imagination as for an appropriate vocabulary in which boundaries are parameters, parts are components, things are not equal but co-equal, [and] signs are indicators. . . . To know oneself is to have self-awareness, communities being studied are target areas, thinking is conceptualization, patterns are configurations, and people do not speak but articulate or verbalize; nor are they injured: they are traumatized. . . .
>
> You can move on quickly to more complex constructions. "Siblings are conflicted in their interpersonal relationships" means that children of the same parent or parents don't like each other. "Exogenous variables form the casual linkage that explains the poverty impact, the behavior modification, and the intergroup dissonance in the target area" means that outside factors cause the poverty and the changes in people that lead to trouble in the neighborhood. A recommendation by a medical ethicist that a physician obtain an input from the patient's own value system means that the patient should be asked whether he wants the treatment. (pp. 146-147)

We don't mean to discourage the use of professional terminology when it is called for; we only urge that your writing be clear, simple, and direct. The use of jargon may muddy your message.

GRAMMAR AND SYNTAX

The mighty comma! This little piece of punctuation has the power to change the entire meaning of a sentence. *The counselor trainee the supervisors observed was having difficulty in applying behavior modification techniques* means that the supervisors observed a particular trainee who was having this difficulty. *The counselor trainee, the supervisors observed, was having difficulty in applying behavior modification techniques.* The commas give a completely different connotation to the word *observed.* Without the commas, *observed* is being used in the sense of "saw" or "watched"; with the commas, it means "made an observation" or "said."

Here's a case in which the meaning is clear, but only after a second reading of the sentence. *The group counseling sessions are cancelled today and tomorrow classes will start late.* These are two independent clauses separated by a conjunction; this construction almost always requires a comma. Without a comma after *today,* the reader tends to link *today* and *tomorrow* before realizing the writer's intent. But be careful; what appear to be independent clauses may not be. *The group counseling sessions are cancelled today, and tomorrow will resume as usual.* We're all relieved to hear that, but the writer intended no such assurance. Two independent clauses have two subjects and two verbs. This sentence has one subject *(sessions)* and a compound verb *(are cancelled* and *will resume); tomorrow* is an adverb. The best way to rewrite the latter sentence is *The group counseling sessions are cancelled today and will resume tomorrow as usual.*

Pronouns without clear antecedents are inevitably confusing. *The teachers put the children's drawings on the walls, and the parents praised them for their originality.* It's not clear what the pronouns *them* and *their* refer to. The situation calls for either a repetition of the noun being referred to or a recasting of the sentence. The second clause should be either *the parents praised the children's originality* or *the parents praised the originality of the drawings* or *the parents praised the teachers for the originality of their idea.* We assume that the walls were secure enough not to crumble for lack of parental praise.

Syntax refers to the order and relation of the elements of a sentence. *Dr. Finch was among the department heads at the meeting.* If Dr. Finch is one of the department heads, the sentence would be better written *Dr. Finch was one of the department heads at the meeting.* If Dr. Finch was standing amidst a group of department heads, that should be made clear: *Dr. Finch was standing among the department heads at the meeting.* Another example of a syntactical problem: *The concept of psychological education in the university has changed drastically* must be changed to read either *In the university, the concept of psychological education has changed drastically* or *Psychological education in the university is a concept that has changed drastically.* A third example: *Wives had a greater desire to talk to a counselor than their husbands,* said one author, making it easy to see why the wives

---

" 'Wives had a greater desire to talk to a counselor than their husbands', said one author, making it easy to see why the wives needed counseling."

---

needed counseling in the first place. What the author meant was: *Wives, more than their husbands, wanted to talk to a counselor.* Another alternative: *Wives had a greater desire to talk to a counselor than did their husbands.*

The program included lectures on the rationale for career development and role playing. There are three possible meanings here, and the syntax of the sentence should leave no doubt as to which is correct. *The program included lectures on the rationale for career development and the rationale for role playing.* Or, *The program included role-playing exercises and lectures on the rationale for career development.* Or, *The program included lectures on role playing and on the rationale for career development.* The difficulty in the original sentence arises from the fact that the reader can't tell whether the noun *role playing* is the object of the preposition *on,* the object of the preposition *for,* or the direct object of the verb *included.*

The placement of adjectives can be critical. In the phrase *new students, faculty, and staff,* it isn't clear whether *new* refers to all three groups or to students only. If the writer means to refer to all three groups, the phrase can read either *new students, new faculty, and new staff* or *students, faculty, and staff, all of whom were new.* If *new* refers to students alone, it can read, *new students, the faculty, and the staff* or, even better, *faculty, staff, and new students.*

Our intention here was not to write a grammar and style book but to focus on some common faults that hamper readability. Be aware of these faults. Look for others as well. Be a critical reviewer of your own writing; question every word, every phrase, every sentence. But don't stop there. Since you, as an author, may be too close to your own writing to be able to look at it objectively and assess its quality, have someone else read and critique it. That someone should be a person outside your professional field, a person who can provide an honest and objective appraisal of your writing. An English instructor, a writer, or an editor would be ideal. And there are plenty of good books on style and usage, some scholarly, some entertaining, all informative and helpful. You'll find our favorites listed in the bibliography.

A FINAL WORD

Writing quality may be the deciding factor in a journal editor's accepting or rejecting a manuscript. In some cases a manuscript is of borderline acceptability in terms of content and originality, and if the writing is poor, that may be the factor that consigns it to the rejection pile. In other instances a manuscript is quite good with regard to content and originality but is so poorly written that an editor rejects it for that reason alone. A practitioner may indeed have a practical and workable technique, a truly innovative program, or a fresh insight into an accepted theory, but an editor may never discover it. It is unlikely that an editor who has to wade through context to get to content will be favorably disposed toward the material.

We have two suggestions. The first we've mentioned or implied as often as we could in this article: *Economize in expression.* In writing, there is no substitute for simplicity. The second suggestion, closely related to the first, is this: *Write the way you talk.* People don't usually talk in five-syllable words and multiclause sentences; and readers are, after all, seeing the written words of someone who is talking to them. Here's how to check it out: If you would feel uncomfortable saying aloud something you have written, your writing is probably stilted and unnatural. Say to yourself what you would say to another person, and then write it that way. You can do the polishing later.

And so, as we wend our wandering way toward that big editorial office in the sky, we fight with never-ending zeal to extirpate obfuscation and illuminatively elucidate the methodological method for ameliorating the causative determinants of linguistic malfeasance. . . .

BIBLIOGRAPHY

American Psychological Association: Publication manual of the American Psychological Association, (2nd ed). Washington, DC. Author, 1974

Copperud RH: A dictionary of usage and style. New York, Hawthorn, 1967

Newman E: Strictly speaking: Will America be the death of English? Indianapolis, Ind. Bobbs-Merrill, 1974

Perrin PG: Writer's guide and index to English, (5th ed). Glenview, Ill. Scott, Foresman, 1972

Strunk W Jr, White EB: The elements of style, (2nd ed). New York, Macmillan, 1972

University of Chicago Press: A manual of style, (12th ed, rev). Chicago, Author, 1969

Wall J: Getting into print in P&G: How it's done. Personnel and Guidance Journal, 52:594-602, 1974

The Interaction Between d-Tubocurarine, Pancuronium, Polymyxin B, and Neostigmine on Neuromuscular Function

LINDA S. VAN NYHUIS, AB*
RONALD D. MILLER, MD†
RICHARD P. FOGDALL, MD‡
San Francisco, California§

The interaction between pancuronium, d-tubocurarine, polymyxin B, and neostigmine was studied in the rat diaphragm-phrenic nerve preparation. Polymyxin B (5 μg/ml) did not affect twitch tension alone but decreased the pancuronium ED_{50} from 0.8 μg/ml to 0.32 μg/ml and the d-tubocurarine ED_{50} from 0.25 μg/ml to 0.15 μg/ml. Neostigmine (0.2 to 10 μg/ml) antagonized pancuronium or d-tubocurarine-induced depression of twitch tension. In contrast, neostigmine (0.001 to 0.2 μg/ml) augmented polymyxin B depression. Similarly, neostigmine (0.1 μg/ml) augmented combined polymyxin B-pancuronium or polymyxin B-d-tubocurarine depression of twitch tension. The authors conclude that polymyxin B potentiates the neuromuscular blockade from pancuronium or d-tubocurarine and that neostigmine further augments this block.

THE incidence of postoperative infections of the peritoneal cavity and surgical wounds may be decreased by irrigation with polymyxin B.[1-3] However, polymyxin B produces a neuromuscular blockade which neostigmine does not antagonize and may prolong.[1-3] Although neostigmine is an effective antagonist of d-tubocurarine (hereinafter "tubocurarine") or gallamine neuromuscular blockade,[4] it is not known whether neostigmine will antagonize combined block from both polymyxin B and tubocurarine or gallamine.

A recent case report[5] suggested that neuromuscular blockade from polymyxin B-pancuronium was enhanced rather than antagonized by neostigmine. This also was the first report of pancuronium block being prolonged by polymyxin B. Accordingly, we studied the neuromuscular interaction between pancuronium, tubocurarine, polymyxin B, and neostigmine.

METHODS

Hemidiaphragms with attached phrenic nerves were resected from exanguinated 250-gm male Sprague-Dawley rats.[6] The preparations were placed in a 50-ml bath of Tyrode's solution[7] at 27 C (pH 7.1). One end of the diaphragm was fixed and the other end attached to a force-displacement transducer. The nerve was stimulated supramaximally (duration = 1 msec; frequency 0.2 Hz) and resultant muscle twitches, which

*Staff Research Associate, Department of Pharmacology.
†Associate Professor, Department of Anesthesiology/Pharmacology.
‡Research Trainee, Department of Anesthesiology.
§University of California Medical Center, San Francisco, California 94143.
Presented in part at the 1975 ASA meeting, Chicago, Illinois.
Reprint request to: Dr. Miller.
This study was supported in part by USPHS Grants 5T1 GM0063-17 and 1P01 GM155561-07.
Paper received: 5/30/75
Accepted for publication: 6/20/75

were calibrated with weights, were recorded on a polygraph. Dose-response curves were obtained for neostigmine (N=6), polymyxin B (N=6), pancuronium (N=4), and tubocurarine (N=4) alone. Also the effect of neostigmine on either a polymyxin B (N=4), pancuronium (N=6), or tubocurarine (N=6) neuromuscular blockade was determined.

Lastly, the effect of neostigmine on either polymyxin B-pancuronium (N=5) or polymyxin B-tubocurarine (N=5) neuromuscular block was determined. Drugs were added to the bath only after the twitch had been stable for 10 minutes. Maximum depression of twitch tension was observed for at least 5 minutes, to insure a stable endpoint. Then, at least three washings were used to remove the drug from the bath.

When the twitch tension had returned to control for at least 10 minutes, the process was repeated until a complete dose-response curve was obtained. The order of drug dose administration was randomized.

Linear regression lines were compared by analysis of variance.[8]

RESULTS

Without other drugs present, smaller doses of neostigmine (0.3 to 0.5 μg/ml) increased and larger doses (1 to 2 μg/ml) decreased twitch tension (fig 1). The ED_{50} dose (the dose resulting in a 50 percent reduction in twitch tension) of polymyxin B was 23 μg/ml (fig 2). Polymyxin B (5 μg/ml) decreased the ED_{50} of pancuronium

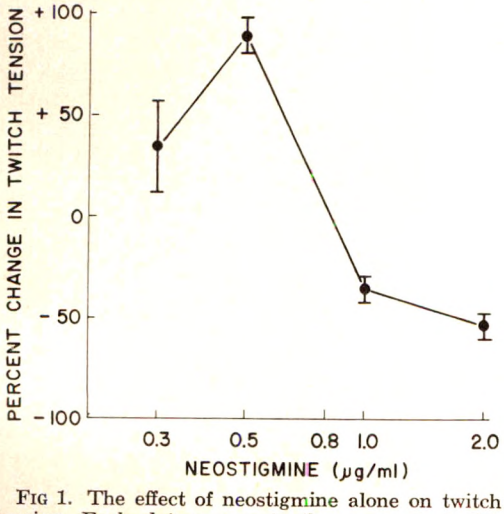


FIG 1. The effect of neostigmine alone on twitch tension. Each dot represents the mean ± 1 SE. (N = 6)

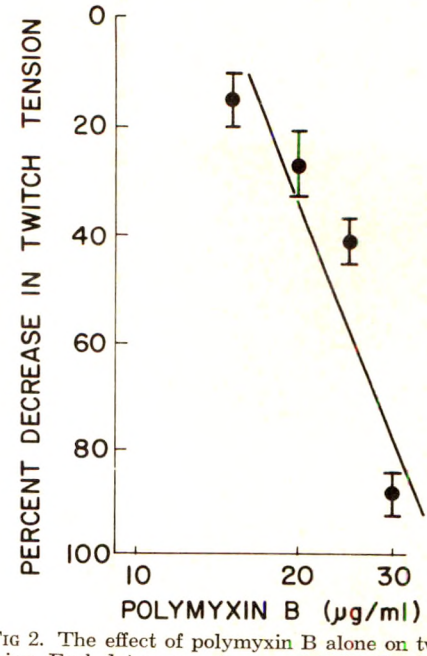


FIG 2. The effect of polymyxin B alone on twitch tension. Each dot represents mean ± 1 SE. The N = 6 on all doses except the 15 μg/ml dose, of which N = 4. ($r = 0.73$)

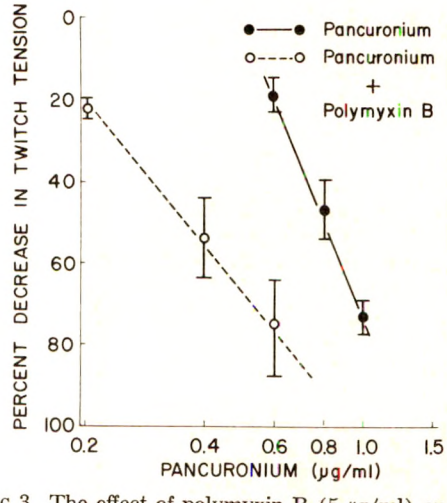


FIG 3. The effect of polymyxin B (5 μg/ml) on a pancuronium dose-response curve. The correlation coefficient for the pancuronium curve is 0.84 and for the pancuronium plus polymyxin B curve is 0.82. (N = 4)

from 0.8 to 0.32 μg/ml ($p<0.01$) (fig 3). Polymyxin B (5 μg/ml) decreased the ED_{50} of tubocurarine from 0.25 to 0.15 μg/ml ($p<0.01$) (fig 4). Although the pancuronium and pancuronium-polymyxin B dose-response curves were not completely parallel ($p<0.05$), the tubocurarine and tubocurarine-polymyxin curves were parallel.

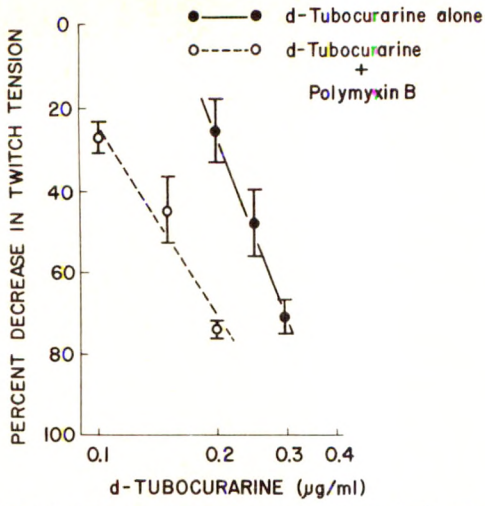


FIG 4. The effect of polymyxin B (5 μg/ml) on a tubocurarine dose-response curve. The correlation coefficient for the tubocurarine curve is 0.93 and for the tubocurarine-polymyxin B curve is 0.88. (N= 4)

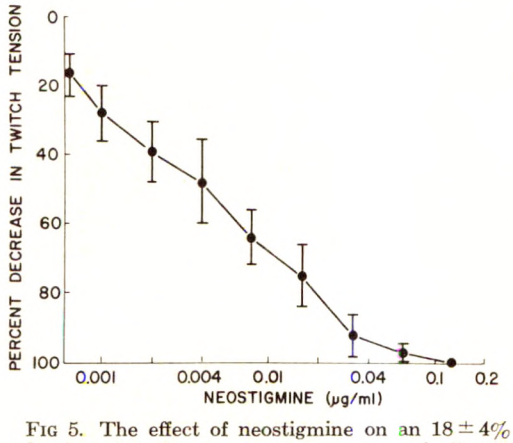


FIG 5. The effect of neostigmine on an 18 ± 4% reduction of twitch tension from polymyxin B (15 μg/ml). Each dot represents the mean ± 1 SE. (N= 4)

Neostigmine (0.001 to 0.15 μg/ml) progressively enhanced an 18 ± 4 percent block from polymyxin B (fig 5). In contrast, neostigmine (0.2 to 10 μg/ml) progressively antagonized a 73 ± 5 percent tubocurarine and 84 ± 5 percent pancuronium-induced depression of twitch tension (fig 6).

When polymyxin B (5 μg/ml) and pancuronium (0.3 μg/ml) were added to the bath, a 35 ± 9 percent reduction of twitch tension occurred. Neostigmine (0.1 μg/ml) which previously antagonized pancuronium block, enhanced the block such that by 130 minutes, a 90 percent reduction in twitch tension had occurred (fig 7). Similarly, neostigmine also augmented polymyxin B-tubocurarine block. When polymyxin B (5 μg/ml) and tubocurarine (0.2 μg/ml) were added to the bath, an 82 ± 2 percent depression of twitch tension followed. Although initial antagonism occurred, neostigmine (0.1 μg/ml) augmented the block such that a 100 percent depression of twitch tension occurred by 50 minutes (fig 7).

DISCUSSION

Our results confirm the clinical observations that polymyxin B potentiates the neuromuscular blockade produced by pancuronium and tubocurarine.[5] Polymyxin B (5 μg/ml) did not depress the twitch itself, but markedly shifted the dose-response curves of both pancuronium and tubocurarine to the left. Also, neostigmine augmented rather than antagonized a combined polymyxin B-pancuronium or polymyxin B-tubocurarine neuromusclar block.

Although tubocurarine is one-fifth to one-tenth as potent as pancuronium in most species,[9,10] pancuronium is less potent than tubocurarine in the rat. Consonant with previous studies in the rat diaphragm-phrenic nerve preparation,[10] we found that the ratio between tubocurarine and pancuronium ED_{50} was 0.25 μg/ml/0.8 μg/ml, or 0.31. The *in vitro* results here were performed at 27 C and a pH of 7.1, which are ideal for the rat diaphragm-phrenic nerve preparation. In spite of these low values, the similarity between our results and the clinical observations of Fogdall and Miller[5] suggests that the results of this study apply also to man. Additional *in vivo* studies at higher temperatures and pH are needed for confirmation.

The mechanism by which polymyxin B depresses neuromuscular transmission never has been elucidated. Our results indirectly suggest that polymyxin B does not act by the classic depolarizing, nondepolarizing, or desensitization methods. A depolarizer would be augmented by neostigmine but should antagonize tubocurarine.[11,12] Conversely, a desensitizer or nondepolarizer should augment tubocurarine but be antagonized by neostigmine.[11,12] Clearly, polymyxin B does not fit either classification.

The bactericidal activity of polymyxin B results from an interaction with cell membrane phosphatidylethanolamine, causing an irreversible breakdown in the permeability barriers of the membrane.[13] Such an action on nervous tissue (which has a high phos-

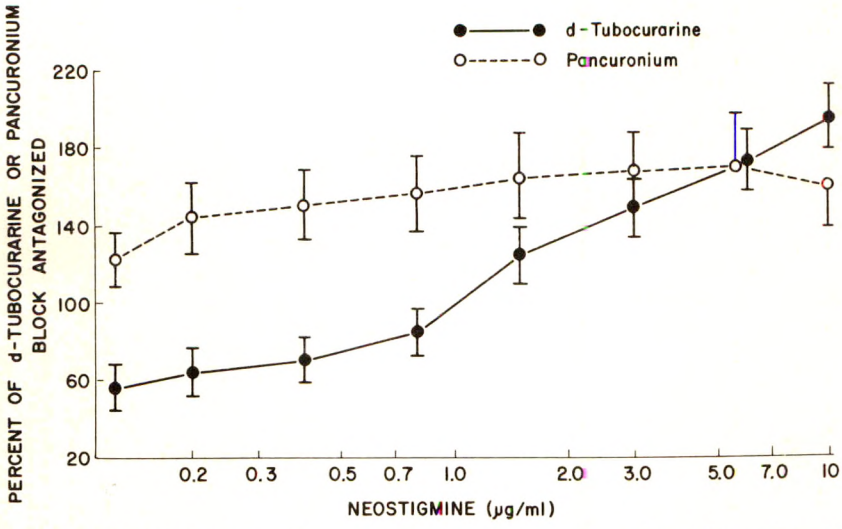


FIG 6. The effect of neostigmine on a pancuronium or tubocurarine-induced depression of twitch tension. The initial pancuronium (1 μg/ml) depression was 84 ± 5% and tubocurarine (0.3 μg/ml) was 73 ± 5%. (N = 6)

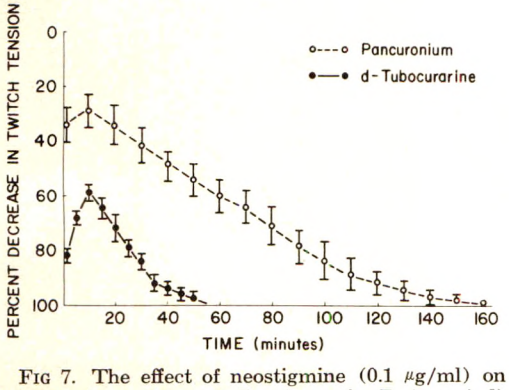


FIG 7. The effect of neostigmine (0.1 μg/ml) on pancuronium (0.3 μg/ml)-polymyxin B (5 μg/ml) induced 35 ± 9% and tubocurarine (0.2 μg/ml)-polymyxin B (5 μg/ml) induced 82 ± 2% depression of twitch tension. (N = 5)

phatidylethanolamine content) or on muscle would reduce their transmembrane potentials. A generalized decrease in transmembrane potential could impair transmitter release, postsynaptic depolarization, and muscle contractility. Obviously, microelectrode studies are required to explore these possibilities.

It is routine practice clinically to administer neostigmine to antagonize a nondepolarizing neuromuscular blockade from pancuronium or tubocurarine. However, in the presence of polymyxin B, neostigmine may actually augment the block, and such a neuromuscular blockade should be allowed to terminate spontaneously with ventilation controlled. Practically, it is difficult to determine how much of the block is from polymyxin B or nondepolarizing relaxant. We administer 2.5 mg/70 kg of neostigmine initially. If the block persists, we do not administer additional neostigmine but allow the block to terminate spontaneously which may take several hours.

REFERENCES

1. Timmerman JC, Long JP, Pittinger CB: Neuromuscular blocking properties of various antibiotic agents. Toxicol Appl Pharmacol 1:299-304, 1959

2. Adamson RH, Marshall FN, Long JP: Neuromuscular blocking properties of various polypeptide antibiotics. Proc Soc Exp Biol Med 105:494-497, 1960

3. Naiman JG, Martin JD Jr: Some aspects of neuromuscular blockade by polymyxin B. J Surg Res 7:199-206, 1967

4. Miller RD, Larson CP Jr, Way WL: Comparative antagonism of d-tubocurarine, gallamine, and pancuronium neuromuscular blockades by neostigmine. Anesthesiology 40:84-87, 1974

5. Fogdall RP, Miller RD: Prolongation of a pancuronium-induced neuromuscular blockade by polymyxin B. Anesthesiology 40:84-87, 1974

6. Bulbring E: Observations on the isolated phrenic nerve-diaphragm preparation in the rat. Brit J Pharmacol 1:38-61, 1946

7. Rudin SG, Foldvari TL, Levy CK: Bioinstrumentation, Experiments in Physiology. Millis, Massachusetts, Harvard Apparatus Foundation, Inc, 1971, p 105

8. Snedecor GW: Analysis of covariance, Statistical Methods. Ames, Iowa, Iowa State University Press, 1971, pp 419-446

9. Miller RD, Way WL, Dolan WM, et al: Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. Anesthesiology 35: 509-514, 1971

10. Buckett WR, Marjoribanks CEB, Marwick FA, et al: The pharmacology of pancuronium bromide (ORG NA 97), a new potent steroidal neuromuscular blocking agent. Brit J Pharmacol 32:671-682, 1968

11. Gissen AJ, Katz RL, Karis JH, et al: Neuromuscular block in man during prolonged arterial infusion with succinylcholine. Anesthesiology 27: 242-249, 1966

12. Jenkinson DH: The antagonism between tubocurarine and substances which depolarize the motor end-plate. J Physiol 151:309-324, 1960

13. Hsu Chen CC, Feingold DS: The mechanism of polymyxin B action and selectivity toward biological membranes. Biochemistry 12:2105-2111, 1973

AGE, LIVER DISEASE AND DIAZEPAM The separate effects of increasing age or hepatocellular liver disease on diazepam pharmacokinetics were evaluated. In normal patients, following 0.1 mg/kg intravenously or 10 mg orally, the terminal diazepam half-life increased linearly with age from about 20 hours at 20 years to about 90 hours at 80 years. This change was not due to differences in drug metabolizing activity or plasma protein binding but correlated with the initial distribution volume of the drug. Despite the prolonged half-life, the constancy of plasma clearance despite age suggests drug accumulation is no more likely in the elderly than the young patient. Severe liver disease was associated with more than a two-fold increase in diazepam half-life due primarily to reduced plasma clearance (biotransformation) of the drug. Biochemical tests of liver function did not adequately reflect the ability of the diseased liver to metabolize diazepam. Thus, chronic diazepam administration to patients with liver disease might result in cumulative effects. *(Klotz U, Avant GR, Hoyumpa A et al: The effects of age and liver disease on the disposition and elimination of diazepam in adult man. J Clin Invest 55:347-359, 1975)*

Incidence of Prolonged Pain Relief Following Acupuncture

PETER K. Y. LEE, MD*
JEROME H. MODELL, MD†
THORKILD W. ANDERSEN, MD‡
SEGUNDINA A. SAGA, MD§
Gainesville, Florida‖

From March 1973 to December 1974, 2090 electroacupuncture treatments were applied to 533 patients with chronic pain. Of 533 patients, 276 (52%) reported excellent (>75%) pain relief immediately after the last treatment, and 103 (19.3%) still reported excellent pain relief on a 4-week follow-up questionnaire. In March 1975, the authors contacted 87 of these 103 patients. Sixty-three reported that they still had excellent pain relief 3 to 18 months after therapy, 3 patients reported that their pain still was relieved 50%, and 21 patients said their pain had returned to the same intensity as before therapy. Thus, 12% of 533 patients who received acupuncture treatment for chronic pain had a significant degree of pain relief at least 3 months after therapy.

WE PREVIOUSLY reported on 261 patients who received up to 4 consecutive acupuncture treatments for chronic pain.[1] In that study, 133 patients were treated with electrically stimulated needles placed in traditional acupuncture meridians. The remaining 128 patients also received electrical-needle stimulation; however, these had been placed alternately in traditional meridians and in arbitrary locations. We found that 117 patients (54%) reported that their pain was either relieved completely or had decreased in intensity by at least 75% immediately after the 4th treatment. In a 4-week follow-up questionnaire, 47 (18.6%) of the 252 patients who responded still had at least 75% relief from pain.[1] Needle placement did not influence the results in that study. We have continued to study patients using this modality, to determine the incidence of long-term pain relief. The purpose of this report is to identify those patients who received relief from pain for more than 3 months after acupuncture therapy.

METHODS

Between March 1973 and December 1974, 2090 acupuncture treatments were applied to 533 patients suffering from chronic pain. All patients received 3 treatments on successive days and most returned for a 4th treatment. Results of the 4-week follow-up were reported previously in 252 patients (9 patients did not answer the 4-week questionnaire).[1] The remaining 272 patients were treated similarly with needles being placed at traditional meridian points. These have not been reported. Electroacupuncture was performed via 27-gauge hypodermic needles by an electric stimulator with 0.35 ms pulse width; biphasic-capacitor-coupled square wave; pulse rate 10 to 300/sec; and

*Visiting Research Professor.
†Professor and Chairperson.
‡Professor.
§Assistant Professor.
‖Department of Anesthesiology, University of Florida College of Medicine, J. Hillis Miller Health Center, Gainesville, Florida 32610.

Paper received: 7/10/75
Accepted for publication: 8/14/75

amplitude 0 to 12 volts variable control. The adjustable controls were set to 200 pulses/sec and 3 volts. The amplitude was further adjusted according to individual tolerance. We did not include patients who were known narcotic addicts or who were in the course of compensation settlement.

Patients interviewed for subjective degree of pain relief by someone not involved in administering the acupuncture were asked to grade the degree of relief as 0, 25, 50, 75, or 100%. Follow-up was in person, by mail, and by telephone.

RESULTS

Of 533 patients, 276 (52%) reported excellent (>75%) pain relief immediately after the last treatment and 103 (19.3%) still reported excellent pain relief on the 4-week posttherapy questionnaire. In March 1975, we contacted 87 of these patients either by a 2nd questionnaire or by telephone. (We were unable to reach the remaining 16 patients.) Of these, 21 patients reported that their pain had returned to the same intensity as before therapy; 63 still had >75% degree of pain relief at 3 to 18 months after therapy; and 3 patients reported their pain still to be relieved 50%. Thus, 12% of the patients contacted had residual pain relief (table 1).

As in our previous study, there was no significant difference in the incidence of pain relief whether the needle placement was in traditional meridian locations or in arbitrary control points.

TABLE 1
Duration of Relief of Pain Following Acupuncture

Duration	Number of patients
100% relief	
3 to 5 months	16
6 months	7
7 to 9 months	8
11 to 18 months	9
Total	40
75% relief	
3 to 6 months	10
7 to 12 months	8
15 to 18 months	5
Total	23
50% relief	
3 months	1
11 months	2
Total	3

TABLE 2
Duration of Pain Prior to Acupuncture Treatment

Duration	Number of patients
6 to 12 months	9
2 to 5 years	30
7 to 8 years	5
10 to 15 years	12
20 to 40 years	10
Total	66

Of the 66 patients who reported pain relief at least 3 months after therapy, 9 had suffered from pain for less than 1 year before therapy, 35 reportedly suffered from pain from 2 to 8 years, and 22 stated that they had been in pain for at least 10 years (table 2). Thirteen patients had resumed pain medications but in smaller doses than previously used. The remaining 53 patients were no longer taking pain medication. The pretreatment diagnoses of these 66 patients are shown in table 3. Thirty-four patients were male and 32 were female, with a mean age of 61.3 ± 14 years.

DISCUSSION

Neither the mechanism of chronic pain nor the mechanism of acupuncture is fully understood. Thus, treating chronic pain with acupuncture is analogous to a blind person riding a blind horse. Yet, there are numerous testimonials of acupuncture therapy relieving the pain of low back discomfort, arthritis, neuralgia, and headache.[1-6] Of the 533 patients treated in our study, all had been treated previously with drugs and many had been treated surgically. When pain persisted, patients sought acupuncture as an alternative to conventional modes of therapy. While 52% of patients reported at least 75% relief of pain immediately after their last acupuncture treatment, pain returned to many. However, 4 weeks later, 19.3% of patients still had excellent pain relief.

Although the incidence of pain relief fell considerably between the last treatment and the 4-week follow-up, the majority of patients who still had significant pain relief

TABLE 3
Diagnosis of 66 Patients Who Received Long-Lasting (3 to 18 Months) Relief Following Acupuncture Treatment*

Diagnosis	Number of patients
Low back pain	
Post disc surgery; laminectomy/fusion	10 (105)
Unknown etiology	7 (73)
Degenerative disc disease	2 (21)
Spondylolisthesis	2 (21)
Total	21 (220)
Osteoarthritis, spine/extremities	17 (122)
Neuralgia	
Postherpetic	2 (6)
Postsurgery	3 (10)
Postinjection	2 (6)
Tic douloureux	2 (9)
Peripheral neuropathy	1 (2)
Total	10 (33)
Headache	
Migraine	3 (12)
Cervical arthritis	1 (4)
Tension headache	1 (4)
Cause unknown	2 (10)
Total	7 (30)
Traumatic arthritis	6 (16)
Other	5 (112)

*Number in brackets is total patients in each entity.

4 weeks after therapy experienced this relief for at least 3 months. While immediate relief of pain after acupuncture therapy may be a poor indicator of long-term results, our experience suggests that the majority of the patients who have pain relief for at least a month can look forward to long-term effectiveness.

Since there was no difference between those patients who received their therapy along traditional meridians and those who received needles at arbitrarily selected points, we question whether the results of our study represent the results of "acupuncture" or the results of "counterstimulation." Our study was not designed to offer an explanation of the mechanism by which our patients obtained pain relief. However, we did attempt to study the placebo effect by placing needles in other than the traditional meridians. This portion of our study suggests that electrical stimulation at traditional meridians was unimportant. However, if the effectiveness of therapy is due to counterstimulation, this, too, would be produced by the electrical stimulation of the needles in the arbitrary control points. Thus, it was impossible for us to separate a placebo effect from this mechanism.

ACKNOWLEDGMENT

The authors thank Ms. Sherry Kamradt and Mr. Daniel Roberson for their assistance in retrieving the follow-up data.

REFERENCES

1. Lee PK, Andersen TW, Modell JH, et al: Treatment of chronic pain with acupuncture. JAMA 232:1133-1135, 1975

2. Barke MW: A retrospective study of acupuncture. Am J Acupunc 2:88-93, 1974

3. Kim DC, Yount RA: The effect of acupuncture on low back pain. Am J Chin Med 2:421-428, 1974

4. Lawrence RM: Acupuncture for the treatment of headache. A preliminary report. Am J Acupunc 2:105-108, 1974

5. Leung SJ: Acupuncture treatment of pain syndrome. Part I. Treatment of sciatica. Am J Chin Med 1:317-326, 1973

6. Weiss SL: Management of low back pain syndromes with acupuncture. Am J Acupunc 2:180-184, 1974

Circulatory Changes in Patients with Coronary Artery Disease Following Thiamylal-Succinylcholine and Tracheal Intubation

ROBERT K. STOELTING, MD*
CHRISTINE PETERSON, RN†
Indianapolis, Indiana‡

Circulatory responses after thiamylal (4 mg/kg) and succinylcholine (SCh) (2 mg/kg) administration followed by direct laryngoscopy and tracheal intubation were measured in 20 patients before elective aortocoronary vein bypass graft operations. Compared with awake measurements, the mean arterial pressure (MAP) decreased 19 ± 3 torr (mean ± SE) and heart rate (HR) increased 9 ± 3 bpm 1 minute after thiamylal-SCh. MAP was increased 39 ± 4 torr and HR 20 ± 3 bpm above awake levels in response to laryngoscopy and tracheal intubation. Blood pressure and HR returned spontaneously to near awake levels without additional anesthesia within 5 minutes of anesthetic induction. Stroke volume index was decreased significantly after tracheal intubation but cardiac index was not altered.

The authors conclude that thiamylal-SCh followed by tracheal intubation is an acceptable anesthetic induction sequence for patients without evidence of left ventricular heart failure who require anesthesia for elective coronary artery revascularization.

A PRIMARY goal in anesthetic management of the patient with coronary artery disease is to minimize alterations in myocardial O_2 requirements and maintenance of coronary blood flow.[1] Barbiturate anesthetic induction may produce decreases in blood pressure that could impair myocardial O_2 delivery, while increased myocardial O_2 needs might result from increased blood pressure and heart rate (HR)[2] during direct laryngoscopy and tracheal intubation. If excessive or persistent, these circulatory changes could adversely alter the ratio of myocardial O_2 delivery to consumption, especially in patients with stenotic coronary arteries.

This study reports the duration and magnitude of circulatory changes after rapid IV thiamylal administration followed by succinylcholine (SCh), direct laryngoscopy, and tracheal intubation in patients with coronary artery atherosclerosis.

METHODS

Twenty adult patients (53 ± 2 years, 78 ± 3 kg, mean ± SE) were studied in the supine position before elective aortocoronary vein bypass graft operations. No patient was included in the study if left ventricular heart failure was considered present. Average left ventricular end-diastolic pressures and cardiac indices (CI) at preoperative cardiac catheterization were 8.6 ± 1.1 torr and 3.1 ± 0.3 L/min/sq m, respectively. No patient had received propranolol for at least 24 hours. Preanesthetic medication was with IM morphine (8 to 15 mg) and scopolamine (0.4 to 0.6 mg) about 60 minutes before arrival in the operating room.

A radial artery and internal jugular vein were cannulated and pressures recorded continuously, as was lead 2 of the ECG. After administering 100% O_2 by face mask for 3 minutes, mean arterial pressure

*Associate Professor of Anesthesiology/Pharmacology.
†Anesthesia Research Nurse.
‡Indiana University School of Medicine, Indianapolis, Indiana 46202.

Paper received: 5/27/75
Accepted for publication: 7/7/75

(MAP), HR, and cardiac output (indocyanine green dye and Beckman Cardiodensitometer) were measured. Stroke volume index (SVI), systemic vascular resistance (SVR), and CI were calculated. d-Tubocurarine (40 mcg/kg) was then administered IV, followed 3 minutes later by 4 mg/kg of thiamylal and then by 2 mg/kg of SCh. All drugs were injected rapidly into a forearm vein through a 5 cm Teflon catheter, followed by 5 ml of flush solution to insure entrance into the circulation.

Ventilation was manually controlled via face mask within 15 seconds following thiamylal-SCh. One minute after thiamylal-SCh administration, laryngoscopy with a straight laryngoscope blade was started and the trachea intubated with a cuffed (low-pressure) orotracheal tube. Just before tracheal intubation, 2 mg/kg of 4% lidocaine was sprayed into the larynx and trachea by a Laryngotracheal Anesthesia Kit. Following intubation, ventilation was controlled with a volume ventilator delivering O_2 until 5 minutes following the thiamylal-SCh. Cardiac output measurements were repeated 3 minutes after anesthetic induction. Data were analyzed by Student's *t*-test, with $p<0.05$ considered significant.

RESULTS

Circulatory responses to anesthetic induction, direct laryngoscopy and tracheal intubation are summarized in table 1. The maximum MAP decrease compared with the awake value was 27 ± 5 torr, 43 ± 3 seconds following thiamylal-SCh. MAP was not less than 60 torr in any patient. One minute after thiamylal-SCh administration, MAP was 19 ± 3 torr less than the awake value and HR was increased 9 ± 3 bpm.

Direct laryngoscopy for tracheal intubation was started 1 minute after thiamylal-SCh administration and lasted 35 ± 3 seconds. This stimulation was associated with a maximum MAP increase of 39 ± 4 torr 5 seconds after completion of laryngoscopy, and by 2 minutes after anesthetic induction, the MAP was decreasing. HR was increased 20±3 bpm above awake levels after tracheal intubation. SVI was decreased ($p<0.05$) after anesthetic induction and tracheal intubation but CI was not significantly altered. MAP and HR decreased after tracheal intubation without additional anesthesia and 5 minutes after thiamylal-SCh were not significantly different from awake values. ST-segment changes, suggestive of myocardial ischemia, were not observed on lead 2 of the ECG in any patient during the 5 minutes after anesthetic induction.

DISCUSSION

Alterations in MAP and HR following thiamylal-SCh induction and tracheal intubation were transient. Therefore, the likelihood of decreased O_2 delivery during reduced perfusion pressure or elevated myocardial O_2 requirements due to increased MAP and HR in response to direct laryngoscopy and tracheal intubation should be minimal. Indeed, ECG evidence of myocardial ischemia was not observed in any patient during this anesthetic induction sequence. Nevertheless, a multiple lead ECG might have revealed ischemic changes that were not apparent from monitoring only lead 2.

The magnitude of MAP and HR changes after thiamylal-SCh administration to patients with coronary artery disease was similar to that in patients without known coronary artery disease but anesthetized in an

TABLE 1
Circulatory Responses to Anesthetic Induction and Tracheal Intubation in Patients with Coronary Artery Disease (mean ± SE)

	Awake	After d-tubocurarine pretreatment	Minutes after thiamylal-SCh (direct laryngoscopy for tracheal intubation starting at 1 minute)			
			One	Two	Three	Five
MAP, torr	111 ± 4	109 ± 4	92 ± 4*	143 ± 6*	130 ± 5*	115 ± 5
HR, bpm	70 ± 3	72 ± 3	79 ± 3*	90 ± 3*	83 ± 3*	79 ± 4
CI, L/min/sq m	2.9 ± 0.2				2.5 ± 0.2	
SVI, ml/beat/sq m	41 ± 2				30 ± 3*	
SVR, torr/L/min/sq m	38 ± 2				52 ± 3*	

*$p < 0.05$.

TABLE 2
Comparison of MAP and HR Measurements With or Without Coronary Artery Disease (mean ± SE)

	Coronary artery disease	Normal[3]
Awake MAP, torr	111 ± 4*	97 ± 3
Lowest MAP after thiamylal-SCh, torr	84 ± 3	76 ± 4
Magnitude of MAP decrease after thiamylal-SCh, torr	27 ± 3	21 ± 2
Highest MAP in response to direct laryngoscopy and tracheal intubation, torr	150 ± 6*	127 ± 6
Magnitude of MAP increase in response to direct laryngoscopy and tracheal intubation, torr	39 ± 4	30 ± 3
Awake HR, bpm	70 ± 3	75 ± 5
Magnitude of HR increase in response to direct laryngoscopy and tracheal intubation, bpm	20 ± 2	24 ± 3

*$p < 0.05$. Coronary artery disease compared with normal.

identical manner (table 2).[3] However, the awake MAP and maximum MAP achieved in response to direct laryngoscopy and tracheal intubation were significantly greater in patients with coronary artery disease.

Impaired left ventricular contractility due to coronary artery disease and/or beta-adrenergic blockade from propranolol might influence the circulatory response to anesthetic induction and subsequent tracheal intubation. Preoperative ventriculograms revealed areas of left ventricular dyskinesis in 4 of our 20 patients. However, circulatory responses were similar to those seen in patients without detectable areas of impaired left ventricular contractility, and the data were pooled for all 20 patients.

With respect to beta-adrenergic blockade, Prys-Roberts and coworkers[4] reported reduced circulatory responses to anesthetic induction (thiopental or Althesin), laryngoscopy, and tracheal intubation in hypertensive patients receiving practolol. However, discontinuing propranolol 24 hours preoperatively, combined with the brief plasma half-life of the drug,[5] makes it unlikely that beta-adrenergic blockade contributed to the circulatory responses observed in our patients.

We conclude that thiamylal-SCh anesthetic induction followed by tracheal intubation was not associated with persistent changes in MAP or HR in patients with coronary artery disease. Furthermore, the magnitude of these changes was similar to that previously demonstrated in patients without known coronary artery disease. Therefore, this would seem an acceptable anesthetic induction sequence for patients requiring anesthesia for elective coronary artery revascularization operations. It must be emphasized that circulatory responses could be different in hypovolemic patients or those with signs of left ventricular heart failure.

REFERENCES

1. Lowenstein E, Bland JHL: Anesthesia for cardiac surgery, Cardiac Surgery. Second edition. Edited by JC Norman. New York, Appleton-Century Crofts, 1972, chapter 4, pp 75-102

2. Katz LN, Feinberg H: The relation of cardiac effort to myocardial oxygen consumption and coronary flow. Circ Res 51:656-669, 1958

3. Stoelting RK, Peterson C: Circulatory changes during anesthetic induction: impact of d-tubocurarine pretreatment, thiamylal, succinylcholine, laryngoscopy and tracheal lidocaine. Anesth & Analg (in press)

4. Prys-Roberts C, Foex P, Biro GP, et al: Studies of anaesthesia in relation to hypertension. V: Adrenergic beta-receptor blockade. Brit J Anaesth 45:671-680, 1973

5. Evans GH, Shand DG: The disposition of propranolol. VI: Independent variation in steady state circulating drug concentrations and half-life as a result of plasma binding in man. Clin Pharmacol Ther 14:494-500, 1973

Failure to Induce Hepatic Pathology in Animals Sensitized to a Halothane Metabolite and Subsequently Challenged with Halothane

J. G. REVES, MD*
LINTON E. McCRACKEN, JR., MD†
Bethesda, Maryland‡

The results of this animal study confirm the induction of delayed hypersensitivity to a halothane metabolite, but the sensitization does not cause hepatic damage on subsequent halothane exposures. Before the hypothesis that hepatic necrosis following halothane has an immunologic basis can be accepted or rejected, more critical studies with different approaches must be made.

POSTOPERATIVE liver dysfunction has been attributed to halogenated anesthetics in a small number of patients. It is postulated in certain susceptible individuals that the anesthetic, or one of its metabolites, acts as a hapten, causing a hypersensitivity reaction that ultimately destroys the liver.[1-3] Other theories that could explain hepatic destruction have been recently reviewed,[4] but hypersensitivity has been the most widely accepted, primarily because of the apparent exacerbation of two cases of hepatitis in anesthesiologists challenged with halothane.[5,6]

The halogenated anesthetics are small and essentially unreactive compounds. The molecular weight of halothane, 197, is considerably less than the smallest immunogenic synthetic molecules, which average 4000 to 5000.[7] Therefore, if there is an immunologic basis for halogenated-anesthetic-induced hepatic pathology, it is most likely the result of the formation of a metabolite that acts as a hapten and combines with autologous protein to form an immunogenic hapten carrier complex. It is unlikely that the inert halothane molecule can itself form a hapten carrier complex.

Trifluoroacetic acid (TFA) is a metabolite of three halogenated anesthetic agents:

*Staff Anesthesiologist.

†Research Fellow.

‡Department of Anesthesiology, National Naval Medical Center, and Naval Medical Research Institute, Bethesda, Maryland.

Dr. Reves' current address is: Department of Anesthesiology, University of Alabama in Birmingham, Alabama 35294.

This study was supported in part by the Bureau of Medicine and Surgery, Department of the Navy, Task Unit #M4306.02.5012, and Ayerst Laboratories, Division of American Home Products Corporation, New York, New York.

The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

The experiments were conducted according to the principles enunciated in "Guide for Laboratory Animal Facilities and Care," published by the United States Department of Health, Education and Welfare, US Public Health Service.

Paper received: 4/14/75
Accepted for publication: 8/4/75

halothane,[8] fluroxene,[9] and isoflurane.[10] Unlike the parent compounds, the products of biotransformation are concentrated in the liver, are chemically reactive, and are capable of forming hapten carrier complexes that could initiate hypersensitivity reactions in the liver. Mathieu's group has demonstrated delayed[11,12] and humoral[13] responses to trifluoroacetylated autologous serum protein in guinea pigs.

Although hypersensitivity can be induced to trifluoroacetylated albumin, it does not mean that this hapten carrier complex is responsible for liver injury following use of the parent compounds. Many diverse compounds complexed to carrier proteins will induce delayed hypersensitivity. The purpose of the experiments reported here was to induce hypersensitivity to trifluoroacetylated homologous serum protein, challenge immunized animals with halothane, and correlate hepatic pathology with the degree of hypersensitivity. Inherent in the study is the question whether the biotransformation product, TFA, complexed to homologous serum protein, is an appropriate antigenic structure to create experimental liver necrosis.

METHODS

Animals.—Twenty-four NMRI(H)* and 53 Dunkin Hartley† guinea pigs of both sexes weighing 350 to 550 gm, fed commercial guinea pig diet and given water containing 2 mg/ml ascorbic acid, were used.

Preparation of Antigens.—Trifluoroacetate was conjugated to guinea pig albumin (GPA) and to human serum albumin (HA) by the method of Goldberger and Anfinsen.[14] Primary reagents were ethyl thioltrifluoroacetate (Pierce Chemical Company, Rockford, Illinois) and human and guinea pig serum albumin (Sigma Company, St. Louis, Missouri).

Samples of the lyophilized trifluoroacetylated protein complexes were sent for fluorine analysis to Schwarzkopf Microanalytical Laboratories, Woodside, New York, and revealed a fluorine content of 4.27% (TFA-GPA) and 4.1% (TFA-HA). The calculated molar ratios were 163 moles fluorine/mole human albumin and 166 moles fluorine/mole guinea pig albumin.

Immunization.—The guinea pigs were divided into three groups. One group received TFA-GPA in doses of 25 to 200 mgm, partially dissolved in physiologic saline solution and then emulsified in complete Freund's adjuvant (CFA) (Difco Laboratory, Detroit, Michigan) which contained 1 mg *Mycobacterium butyricum* per ml of oil. The second group received complete Freund's adjuvant, and the total immunizing dose was divided into four 0.1-ml aliquots, which were injected subcutaneously into each footpad. The third group received similar volumes of saline solution and served as an immunization control.

Skin Tests.—Three weeks after immunization, the flanks were shaved and intradermal injections of antigens administered in 0.1 ml solution of physiologic saline. The antigens tested were: saline, as a nonreactive control; GPA (10 μgm) and HA (10 μgm), as albumin controls; tuberculin purified protein (PPD) (0.1 μgm) to show delayed hypersensitivity response to the CFA; TFA-HA (10 μgm) to test for carrier specificity; and TFA-GPA (10 μgm)—the immunizing compound.

Reactions were observed at 2, 4, 6, 24, and 48 hours and were recorded as either immediate or delayed. Immediate skin reactions were graded at 2, 4, and 6 hours after skin testing based on the following scale:

1—slight edema
2—severe hemorrhage
3—severe edema with necrosis and hemorrhage
4—marked hemorrhage and necrosis

Delayed skin reactions were graded according to the diameter of erythema and induration at 24 and 48 hours after skin testing. Biopsies of the cutaneous reactions were made in three animals 48 hours after testing. The tissue was fixed in 10% formalin buffer and later stained with hematoxylin-eosin (H & E) for microscopic examination.

Halothane Challenge.—Each major group was divided into two subgroups, H and O. Subgroup O was exposed to 100% O_2 and H was exposed to 1% halothane in O_2. The halothane was delivered by a calibrated Fluotec® Mark 2 vaporizer with a 4 L/min O_2 inflow for a period of 2 hours, 3 days after skin testing. The gases were delivered into a 9600 ml clear-plastic box containing two or three guinea pigs. In a series of subsequent experiments, this technic was found to lightly anesthetize the animals but not significantly depress respiration, although hypotension results.[15]

*Naval Medical Research Institute Hartley Strain.
†Perfection breeders.

Liver Study.—The animals were sacrificed five days after halothane exposure. They were stunned by a blow to the head and exsanguinated by cardiac puncture. The liver was examined grossly for any abnormalities, and representative, 5-mm slices from each lobe were placed in 10% formalin buffer. The fixed tissue was then sectioned and stained with H & E for microscopic examination and the degree of fatty change and necrosis scored in the following manner:

1. *Hepatic Necrosis.*—The number of foci of hepatic necrosis were counted on 10 different 40x magnification fields. The fields from each slide were systematically scanned, so that no field was counted more than once. The mean number of foci of necrosis per field was calculated after examining at least three different liver sections from various hepatic sites.

2. *Fatty Changes.*—Fatty changes were scored on a scale of 0 to 4:

0—Less than 20% of all cell cytoplasm contained less than 25% fat.

1—20 to 40% of all cell cytoplasm contained less than 25% fat.

2—40 to 60% of all cell cytoplasm contained 25 to 50% fat.

3—60 to 80% of all cell cytoplasm contained 50 to 75% fat.

4—Over 80% of all cell cytoplasm contained over 75% fat.

All slides were coded so that the observer was unaware of the animal's grouping and treatment.

Statistical Analysis.—Mean, standard deviation, and standard error were calculated on all observations. Mean skin-test scores were compared by analysis of variance. Fatty change and hepatic necrosis between groups was compared by unpaired t-test. Differences between means were considered significant if the calculated p value was 0.05 or less.

RESULTS

Skin Tests.—The results of cutaneous antigen testing at 2, 4, and 6 hours revealed no positive skin reactions to saline, GPA, and HA in all groups. There were occasional positive reactions resulting in erythema and edema in some animals in all groups in response to PPD, TFA-HA, and TFA-GPA. The responses were not significantly different at the 5% confidence level among groups. Responses at 24 hours are shown in table 1. The number of positive responses to TFA-GPA were significantly ($p<0.05$) greater in group I than groups II and III.

Figure 1 demonstrates a typical cutaneous response to TFA-GPA at 24 hours in a group-I animal. Of importance is the highly significant ($p<0.0005$) difference in response of group I to TFA-GPA (23/48) compared to TFA-HA (1/39), a manifestation of carrier specificity. The positive skin reactions to PPD were significantly greater in groups I and II than in group III, which was not immunized with complete Freund's adjuvant. Responses at 48 hours were similar to those at 24 hours, but only responses to TFA-GPA and PPD were significantly greater than other antigens in group I as compared with group III. The degree of response to all antigens at 48 hours was less than at 24 hours.

Liver Studies.—There were no differences in degree of fatty metamorphosis among groups or within subgroups exposed to halothane and not exposed to halothane. Table 2 shows results of fatty change scores in all groups. Small foci of hepatic necrosis were found in many animals, and figure 2 shows

TABLE 1
Number of Positive Cutaneous Reactions 24 Hours After Testing

Antigen	Saline	GPA	HA	TFA-GPA	TFA-HA	PPD
Group I	0/48	10/48	0/47 (1 not tested)	23/48	1/39 (9 not tested)	35/48
Group II	0/11	0/11	0/11	0/11	0/11	4/11
Group III	0/6	0/6	0/6	0/6	0/6	0/6

Responses greater than 5 mm of erythema and induration are positive. HA = human albumin; TFA-GPA = trifluoroacetylated guinea pig albumin; TFA-HA = trifluoroacetylated human albumin. Group I immunized with trifluoroacetylated guinea pig albumin (TFA-GPA) in complete Freund's adjuvant (CFA). Group II immunized with CFA. Group III no immunization.

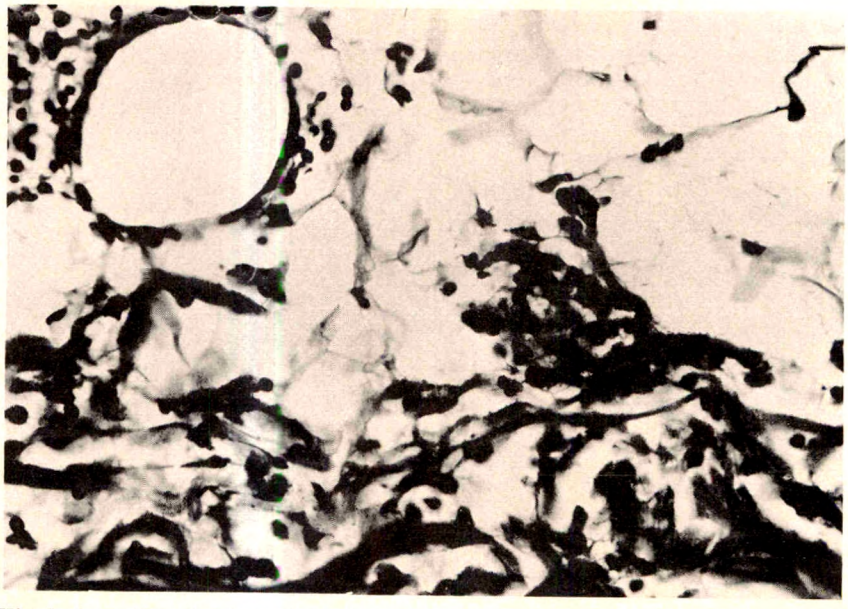


FIG 1. Histologic section showing cutaneous reaction from a guinea pig immunized with 100 μgm trifluoroacetylated guinea pig albumin (TFA-GPA) and tested 3 weeks later with the same complex in saline. The predominant cellular infiltrate is mononuclear and edema is seen in the connective tissue. H & E x 900.

TABLE 2

Scores* of Fatty Changes (± SE) in Guinea Pig Livers

Exposure	Group I	Group II	Group III
Halothane	0.98 ± 0.22 (28)	0.58 ± 0.33 (6)	1.17 ± 0.17 (6)
Oxygen	1.12 ± 0.34 (13)	0.60 ± 0.40 (5)	1.83 ± 0.63 (6)

*Scored 0-4 in increasing severity (see text). Group I immunized with trifluoroacetylated guinea pig albumin (TFA-GPA) in complete Freund's adjuvant (CFA). Group II immunized with CFA. Group III no immunization. Parentheses indicate number of animals in each group.

a representative lesion. Results of the mean number of such foci per 40x microscopic field are presented in table 3 for each group. The foci of necrosis were midzonal and resembled granulomatous areas.

The number of foci was not statistically different among groups or within groups between the halothane-challenged animals and the O_2 controls. There was no discernible difference in type or location of the foci of necrosis in all groups. No areas of massive acute hemorrhagic or coagulative necrosis were observed, nor were mononuclear cellular infiltrates present.

To correlate the degree of delayed hypersensitivity to incidence of focal hepatic necrosis in group I, the 24-hour skin test responses were plotted for each animal with its number of hepatic necrosis foci (fig 3). Using least-square fit analysis, the slopes of group 1-O and group 1-H did not differ from 0 or from each other at the 5% significance level. Therefore, there is no correlation between the degree of skin reaction and number of necrotic foci.

DISCUSSION

Halothane-induced liver injury has been attributed to a hypersensitivity reaction involving autoimmune hepatic destruction. The evidence for this thesis is unconvincing, being based primarily on clinical observations of nonspecific criteria of immune reactions such as fever, rashes, arthralgia, eosinophilia, and an increased incidence of necrosis on repeat exposure to halothane. The most cogent arguments supporting a hypersensitivity process are the two cases of recurring hepatitis in anesthesiologists that followed provocative challenges.[5,6] The history in one of these cases is consistent

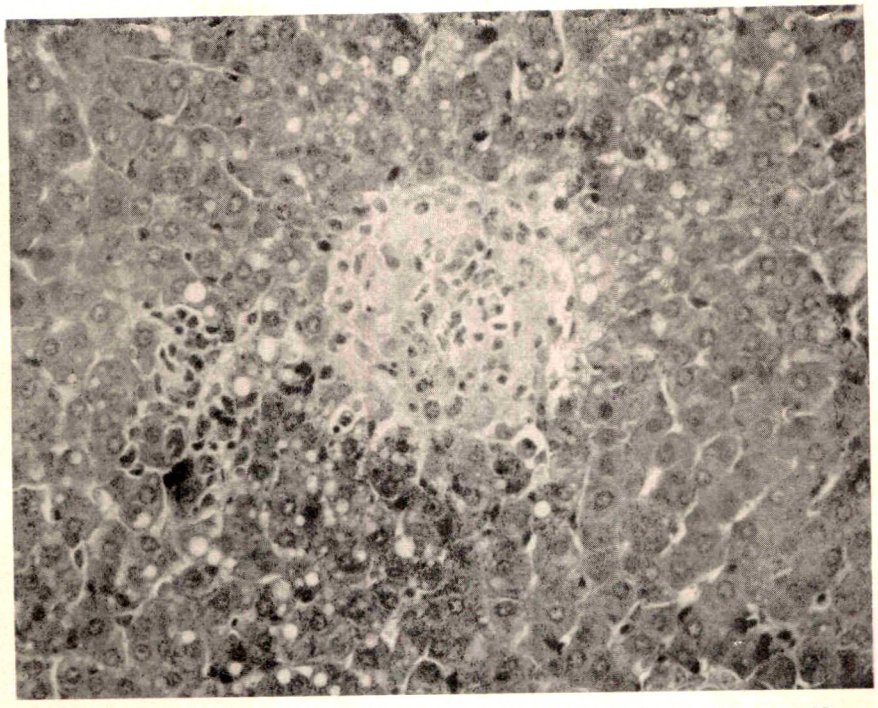


FIG 2. Histologic midzonal section of liver from a guinea pig immunized with 100 μgm trifluoroacetylated guinea pig albumin exposed to 1% halothane/O_2 after 23 days. In the center of normal liver parenchyma is a small focus of coagulation necrosis, distinguished by pyknotic nuclei and homogenous cytoplasm. This lesion is typical of those found in many animals of all groups. H & E x 400.

TABLE 3

Mean Number* (± SE) of Foci of Hepatic Necrosis in Guinea Pig Livers

Exposure	Group I	Group II	Group III
Halothane	1.28 ± 0.81 (28)	0.15 ± 0.10 (6)	1.85 ± 0.48 (6)
Oxygen	0.91 ± 0.24 (13)	0.94 ± 0.61 (5)	0.57 ± 0.37 (6)

*Number of foci of necrosis observed in 40x microscope field. Group I immunized with trifluoroacetylated guinea pig albumin (TFA-GPA) in complete Freund's adjuvant (CFA). Group II immunized to CFA. Group III no immunization. Parentheses indicate number of animals in each group.

with recurrent hepatitis, and has been challenged for this reason.[16]

Although initial reports employing in-vitro lymphocyte stimulation[17] and leukocyte migration methods[18] to detect patients with halothane hepatitis seemed to support a delayed hypersensitivity foundation for the disease, these could not be reproduced.[19,20] The test antigens were halothane or sonicated halothane in serum, and as previously discussed, it is doubtful that this is the appropriate antigen. There have been no well-documented clinical studies demonstrating an immunologic basis as a mechanism for halothane hepatitis.

Since the halothane molecule itself is an unlikely antigen, investigators have postulated that the reactive metabolite, TFA, may complex with autologous protein to form a hapten carrier complex. Experiments have demonstrated that trifluoroacetylated autologous protein can induce hypersensitivity reaction in laboratory animals. Both delayed hypersensitivity mediated by the thymus-lymphocyte (T-cell)[11,12] and immediate reaction involving specific antibody formation[13] have been induced against this hapten carrier complex. The fact that hypersensitivity to a drug metabolite complexed to protein can be induced does not mean

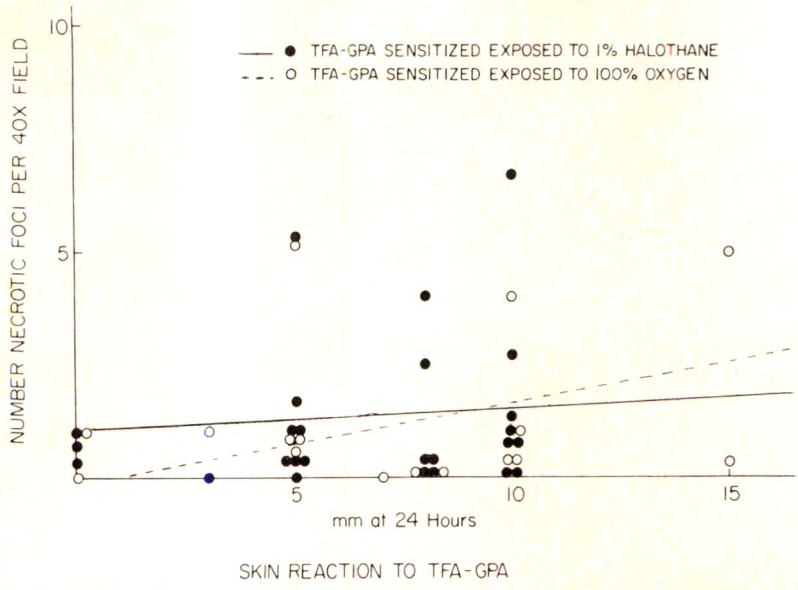


FIG 3. Relation between incidence of foci of necrosis and diameter of skin reaction in guinea pigs immunized with trifluoroacetylated guinea pig albumin. Data from animals exposed to 1% halothane are plotted as closed circles; points from animals exposed to 100% O_2 are shown as open circles. The solid line and dashed line represent the least-square fit of the data derived from halothane-challenged and from O_2-challenged animals, respectively. The slopes of the two groups do not differ significantly from zero or each other.

that this hapten carrier complex causes autoimmune liver destruction.

The data are consistent with those of Mathieu's groups in demonstrating that a delayed hypersensitivity can be induced to TFA-GPA.[11,12] The skin tests show delayed hypersensitivity mediated responses to the antigen. This interpretation is based on the facts that the peak response occurred at 24 hours and that the cellular infiltrate in the biopsied lesions were primarily mononuclear. Also, in support of a delayed response, is the fact that the positive skin test responses were carrier specific, ie, the hapten, TFA, complexed to the autologous carrier protein, GPA, did evoke positive responses, but the same hapten, TFA, complexed to another carrier, heterologous HA, did not cause positive responses in animals sensitized to TFA-GPA.

The second part of the present study addressed the question of hepatic pathology following halothane challenge in animals sensitized to TFA. The data indicate that there is no difference in the number of foci of necrosis found in all groups, whether sensitized to TFA or not. Further, on correlating the degree of delayed hypersensitivity demonstrated by skin test with the incidence of necrosis in the halothane-challenged animals and control O_2-exposed animals of group I, there was no positive correlation and no difference between groups I-H and I-O. Thus it is concluded that sensitization to TFA-GPA followed by halothane challenge does not cause increased hepatic necrosis in the guinea pig.

The presence of foci of hepatic necrosis in all groups (experimental—group I, and controls—groups II and III), as well as the type, degree, and location of necrosis, was similar among all groups. The cause of these lesions is unknown, but the granulomatous nature suggests a subclinical infectious process. Spontaneous lesions in guinea-pig colonies have been reported following infectious processes.[21] Incidence of hepatic fatty changes did not differ among groups or within subgroups. This finding is somewhat at variance with a previous report in which fatty changes were increased in halothane-treated animals compared to O_2 controls.[22] It is impossible to explain this discrepancy, but it should be noted that the present study contains more animals, and the differences between groups in the former study are small.

It would appear from the data that sensitization to a halothane metabolite with subsequent halothane challenge does not

cause hepatic injury. These findings are similar to those reported by Mathieu and coworkers,[23] who sensitized animals to TFA-GPA and demonstrated antibodies (immediate hypersensitivity) against the antigen, but failed to induce increased hepatic pathology after halothane challenge to the animals.

It is important to comment on several considerations about the present experimental model. The guinea pig was chosen because of the report that it was a suitable model for experimental halothane hepatitis[24] and the previous immunologic work in this animal.[11-13] The finding of hepatic lesions in control animals, and the question of whether the guinea pig significantly differs in metabolic or immunologic responses from the human, are valid. The halothane dosage and duration are open to criticism because of the uncertainty of the effects of induced hypotension on the liver;[15,16] however, similar liver pathology was found in O_2 controls, suggesting that decreased perfusion pressure was not responsible for the lesions encountered.

Trifluoroacetic acid is not the sole metabolite of halothane; therefore, other compounds closely related could be the hapten. A reactive intermediary compound, trifluoroacetaldehyde, as recently demonstrated by Van Dyke and Gandolfi to be bound to liver lipoprotein after halothane exposure, is one such compound.[25] Trifluoroacetic acid is a reactive compound and, being by far the largest metabolic product of halothane, would appear the most appropriate to use. However, it is possible that subtle chemical changes among halothane metabolites could alter the immunologic significance of the compounds by alterations in stoichiometric configuration.

A final comment on the present model is the selection of the carrier protein, homologous guinea pig albumin. An alternative carrier protein is autologous liver lipoprotein. Liver lipoprotein normally complexes fatty acids produced in the liver.[26] Two well characterized proteins[27] from cytoplastic fractions of liver have exhibited liver-specific antigenicity. A membrane lipoprotein has been found to inhibit normal migration of leukocytes from patients with autoimmune liver disease (active chronic hepatitis and primary biliary cirrhosis).[28] It is conceivable that TFA or another hapten complexed to this liver-specific lipoprotein might form a hapten carrier complex that constitutes a basis for halothane-induced hypersensitivity and hepatic necrosis.

ACKNOWLEDGMENT

The authors are indebted to Dr. E. Dowdy for her encouragement and aid during the initial experiments and thank Drs. A. Lawton and M. Cooper, Department of Immunology, Birmingham, for their assistance in designing the study. We also thank Drs. R. Tobey, T. Ahmed, and Vanier, Naval Medical Research Institute, for their review of the manuscript, and Ms Linda Porter for her clerical help.

REFERENCES

1. Combes H: Halothane-induced liver damage —an entity. N Engl J Med 280:558-559, 1969

2. Doniach D: Cell-mediated immunity in halothane hypersensitivity. N Engl J Med 283:315-316, 1970

3. Klion FM, Schaffner F, Popper H: Hepatitis after exposure to halothane. Ann Intern Med 27: 467-477, 1969

4. Reves JG: Halothane hepatitis: current concepts. Postgrad Med 56:65-67, 1974

5. Belfrage S, Ahlgren I, Axelson S: Halothane hepatitis in an anesthetist. Lancet 2:1466-1467, 1966

6. Klatskin G, Kimberg DV: Recurrent hepatitis attributable to halothane sensitization in an anesthetist. N Engl J Med 280:515-522, 1969

7. Sela M: Antigenicity: some molecular aspects. Science 166:1365-1379, 1969

8. Rehder K, Forbes J, Alter H, et al: Halothane biotransformation in man: a quantitative study. Anesthesiology 28:711-715, 1967

9. Blake DA, Cascorbi HF: A note on the biotransformation of fluroxene in two volunteers. Anesthesiology 32:560, 1970

10. Hitt BA, Mazze RI, Cousins MJ, et al: Metabolism of isoflurane in Fischer 344 rats and man. Anesthesiology 40:62-67, 1974

11. Mathieu A, DiPadua D, Kahan B, et al: Lymphocyte transformation test, reagenic and complement fixing antibodies in guinea pigs sensitized to a metabolite of halothane and fluroxene. Anesth & Analg 52:676-681, 1973

12. Mathieu A, DiPadua D, Mills J, et al: Experimental immunity to a metabolite of halothane and fluroxene: cutaneous delayed-type hypersensitivity. Anesthesiology 40:385-390, 1974

13. Mathieu A, DiPadua D, Kahan B: Humoral immunity to metabolites of halothane, fluroxene, and Ethrane. Proc Soc Exp Biol Med (in press)

14. Goldberger RB, Anfinsen C: The reversible masking of amino groups in ribonuclease and its possible usefulness in the synthesis of protein. Biochemistry 1:401-405, 1962

15. Reves JG, McCracken LE: Halothane in the guinea pig (letter). Anesthesiology 42:230-231, 1975

16. Simpson BR, Strunin L, Walton B: Evidence for halothane hepatotoxicity is equivocal. Controversy in Internal Medicine. Edited by FJ Ingelfinger, RV Ebert, M Finland, et al. Philadelphia, WB Saunders Company, 1974, vol 2, pp 580-594

17. Paronetto F, Popper H: Lymphocyte stimulation induced by halothane in patients with hepatitis following exposure to halothane. N Engl J Med 283:277-280, 1970

18. Williams WJ, Pioli E, Horton JN, et al: MIF test in halothane jaundice. Br Med J 4:47, 1972

19. Walton B, Dumonde DC, Williams C, et al: Lymphocyte transformation. JAMA 225:494-498, 1973

20. Mathieu A: Diagnosis of halothane hepatitis (letter). JAMA 224:1188-1189, 1973

21. Branch A: Spontaneous infections of guinea pigs. J Infect Dis 40:533-548, 1927

22. Reves JG, McCracken LE: Hepatic pathology and skin test reactions to trifluoroacetylated guinea pig albumin after repeated halothane anesthesia in the guinea pig. Br J Anaesth (in press)

23. Mathieu A, DiPadua D, Kahan BD, et al: Correlation between specific immunity to a metabolite of halothane and hepatic lesions after multiple exposures. Anesth & Analg 54:332-339, 1975

24. Hughes HC Jr, Lang CM: Hepatic necrosis produced by repeated administration of halothane to guinea pigs. Anesthesiology 36:466-471, 1972

25. Van Dyke RA, Gandolfi AJ: Studies on irreversible binding of radioactivity from ^{14}C halothane to rat hepatic microsomal lipids and protein. Drug Metab Dispos 3:51-58, 1975

26. Zimmerman HJ: The spectrum of hepatotoxicity. Perspect Biol Med 12:135-161, 1968

27. Meyer zum Buschenfelde KH, Miescher PA: Liver specific antigens purification and characterization. Clin Exp Immunol 10:89-102, 1972

28. Miller J, Mitchell CG, Eddleston ALWF, et al: Cell mediated immunity to a human liver-specific antigen in patients with chronic hepatitis and primary biliary cirrhosis. Lancet 2:296-297, 1972

FLUROXENE TOXICITY Repeated exposures to fluroxene result in high mortality in all animals species studied to date. Man metabolizes fluroxene differently and toxicity after fluroxene is rare but when it does occur may be associated with a history of drug ingestion capable of producing enzyme induction. The influence of phenobarbital pretreatment on fluroxene toxicity was studied in monkeys since these animals resemble man in biotransformation of xenobiotics. Unlike other animals species, monkeys survived repeated exposures to fluroxene without overt organ toxicity. In contrast, all animals treated with phenobarbital died during fluroxene anesthesia manifesting arterial hypotension and pulmonary edema. It was speculated that phenobarbital increased production of fluroxene metabolites, including the highly toxic trifluoroethanol. The monkey may serve as an animal model to evaluate drug toxicity with and without enzyme induction prior to use in man. *(Munson ES, Malagodi MH, Shields RP et al: Fluroxene toxicity induced by phenobarbital. Clin Pharm Ther 18: 687-699, 1975)*

Atypical Pseudocholinesterase: A Clinical Report

ERWIN LEAR, MD*‖
CASSIM JADWAT, MD†
LUCY BOUGH, MD‡
PAZ FERNANDEZ, MD§
Jamaica, New York‖

The safe conduct of anesthesia demands careful evaluation of the previous experience of patients under anesthesia and surgical operation, as well as that of their families. Untoward responses that may recur with subsequent anesthetic procedures should be documented and patients informed, as the need dictates. Two cases of prolonged apnea following single intubating doses of succinylcholine could not have been predicted by the patient's preanesthetic history. As a result of these problems, the authors recommend more careful preanesthetic history-taking with reference to patients' prior anesthetic experiences.

THE safe anesthetic management of patients depends on the orderly logic of the anesthesiologist as he sorts and analyzes data input from the unconscious patient. It would thus seem incumbent upon the anesthesiologist to study patients carefully when they exhibit unusual responses to the usual conduct of anesthesia.

Prolonged apnea associated with IV drip succinylcholine during operation was reported during the early clinical trials with this drug. While the catabolism of succinylcholine was linked to the enzyme plasma cholinesterase (pseudocholinesterase), other factors have been implicated in a casual relationship to prolonged apnea. It was also noted on occasion that patients experienced significant periods of apnea after receiving a single intubating dose of succinylcholine.

Within the past year, 2 cases of prolonged apnea following single intubating doses of succinylcholine have occurred in one of our hospitals. In each instance, there was no preoperative clue to forewarn us.

CASE PRESENTATIONS

Case 1.—The patient was a 2½-year-old boy weighing 10 kg, admitted for tonsillectomy, adenoidectomy, myringotomy, and bilateral tubal implants. Preoperative physical examination revealed enlarged tonsils and bilateral otitis media but was otherwise noncontributory. The preoperative history as set forth on the chart also was noncontributory except to verify otitis media. No parent was available for further questioning during preanesthesia rounds.

Premedication consisted of 40 mg of pentobarbital and 0.2 mg of atropine IM approximately 1 hour before scheduled operation. The patient arrived in the operating

*Clinical Associate Professor of Anesthesiology, Downstate Medical Center, New York, New York.
†Director of Anesthesiology, Mary Immaculate Hospital Division.
‡Attending Anesthesiologist, Mary Immaculate Hospital Division.
§Erlanger Hospital, Chattanooga, Tennessee.
‖Chairman, Department of Anesthesiology, Catholic Medical Center of Brooklyn and Queens, Inc, Jamaica, New York 11432.
Reprint requests to Dr. Lear, 88-25 153rd Street, Jamaica, New York 11432.
Paper received: 6/13/75
Accepted for publication: 8/13/75

room with a pulse of 140/min, calm and afebrile.

Anesthesia was induced with halothane-N_2O-O_2, 8 L/min, by face mask in a nonrebreathing system. Induction was smooth and 20 mg of succinylcholine was administered IM approximately 8 minutes after induction. Intubation was easily accomplished, ventilation was controlled, and the operation began.

During the 20-minute surgical procedure, vital signs were stable, but the patient remained apneic. Pupils were in midposition and reacted to light. Electrical stimulation of the ulnar nerve produced a minimal twitch response with no tetanus and no posttetanic facilitation; a depolarizing block was apparently still in effect. Blood was drawn for plasma pseudocholinesterase studies. Respiration was still controlled and the endotracheal tube was in place.

The first spontaneous respiratory efforts were observed 3 hours from the time of succinylcholine injection. Another hour passed before tidal volume reached 100 ml, at which time electrical stimulation of the ulnar nerve resulted in an improved twitch response and tetanic response with no posttetanic facilitation. The patient was extubated and discharged to the pediatric floor.

The likelihood of an atypical pseudocholinesterase syndrome was explained to the patient's father, who only then related the following information to us. He had undergone an operation approximately 5 years before and was told that he "took a long time in waking up." Furthermore, the father's mother had a similar experience over 10 years before and consequently was now refusing to undergo biliary surgery out of fear from her prior experience. We could not obtain further information regarding the patient's father or paternal grandmother.

Laboratory results received after the patient's discharge revealed a plasma benzoylcholine rate of 18.8 μmol/hr/ml and a dibucaine number of 21.3 (table), showing the patient to be positive for homozygous atypical pseudocholinesterase. The family, family physician, and surgeon were so notified by mail and family testing recommended. They were advised to notify any physician, surgeon, and anesthesiologist in the future of our findings. The family was also advised orally against exposure to insecticides; this was confirmed in writing to include other cholinesterase inhibitors.

TABLE

Table of Standards*
(μmol/hr/ml plasma at 30° C)

	Mean	
Dibucaine numbers		
Homozygous normal	79	(74-84)
Heterozygous atypical	62	(49-70)
Homozygous atypical	19	(9-27)
Benzoylcholine rates		
Homozygous normal	66	(18-111)
Heterozygous atypical	52	(7-73)
Homozygous atypical	27	(9-48)

*Values from the Anesthesiology Research Laboratory, Montefiore Hospital and Medical Center, Bronx, New York.

Case 2.—The patient was a 52-year-old man weighing 79.9 kg, admitted for repair of a left inguinal hernia. Preoperative physical findings were within normal limits except for his presenting complaint and a right inguinal scar. An ECG was within normal limits. Chest x-ray revealed increased interstitial marking consistent with old granulomatous disease. Past history revealed only that he had undergone a right inguinal herniorrhaphy about 12 years before.

Premedication consisted of 50 mg of meperidine and 0.4 mg of atropine, IM, approximately 1¼ hours before induction of anesthesia. The patient arrived in the operating room calm and awake, with vital signs intact.

Anesthesia was induced with thiopental slowly IV in a 2.5% solution; total dose 300 mg. The patient was oxygenated and 100 mg of succinylcholine administered IV to facilitate intubation, which was accomplished without difficulty. Anesthesia was maintained by halothane-N_2O-O_2 in a semiclosed system.

Intraoperative ventilation was controlled during a 1-hour procedure; no additional relaxant was required. Patient remained apneic for 30 minutes after operation, during which time ventilation was still manually controlled. He began to strain against the endotracheal tube, which was then removed to prevent disruption of the hernia repair. His shallow respiratory efforts were easily assisted via face mask, oral airway, and room air.

The patient was now fully alert but complained of difficulty in spontaneous breathing. His hand grip was noted to be weak

and he was unable to raise his head. Blood-gas analysis revealed the following: Pao_2 98, $Paco_2$ 46, HCO_3^- 24, and pH 7.34. An additional blood sample was drawn for pseudocholinesterase study.

The patient's subsequent course was uneventful. Prior to discharge on the 6th postoperative day, he recalled "spending a long time" in the recovery room following his previous operation of 12 years before. He was then informed of our suspicions and the situation was explained to him, with instructions to await a final written report.

Laboratory findings revealed a plasma benzoylcholine rate of 27.1 μmol/hr/ml and a dibucaine number of 24.9 (table). He was positive for homozygous atypical pseudocholinesterase. As in the previously described case, the significance of these findings was reported to the patient by mail, family test was urged, and others concerned were notified.

DISCUSSION

Prolonged apnea following IV drip succinylcholine for surgical relaxation was observed and studied by early investigators.[1,2] While the role of plasma pseudocholinesterase in the catabolism of succinylcholine was recognized, early investigators were intrigued by the association of bowel surgery and prolonged apnea.

Borders and coworkers[3] took a broader approach to the problem, and in 1955 carried out a well-planned study which determined a multiplicity of events that could contribute to prolonged apnea following IV-drip succinylcholine. Recognizing the degradation of succinylcholine by plasma pseudocholinesterase to be a key factor, these investigators studied a series of hospitalized surgical patients and nonhospitalized individuals; there was no significant difference in their plasma enzyme levels. They identified other events leading to prolonged apnea as controlled ventilation (relative hyperventilation); concomitant use of cyclopropane, which in itself depresses the respiratory centers; and too heavy reliance on muscle relaxant, thus overwhelming the myoneural junction.

One year later, Foldes and associates[4] noted that low pseudocholinesterase levels, as found in patients with liver disease, did not usually cause prolonged apnea. They postulated that such apnea resulted from change in the nature of the neuromuscular block "from a depolarizing to a nondepolarizing" action, which could then be terminated by neostigmine.

Prolonged apnea following single intubating doses of succinylcholine was still not adequately explained, however, until Kalow[5] shed light on the subject with data on the presence of abnormal (atypical) plasma pseudocholinesterase as a genetic variant.

In the patient with the genetic variant of plasma pseudocholinesterase, a single bolus of succinylcholine is only partially hydrolyzed in the blood stream, so that a relatively large percentage of the administered dose overwhelms the myoneural junction. As a consequence, the removal of succinylcholine by diffusion away from the myoneural junction is prolonged. The result is a persistent apnea well beyond the usual 2 to 4 minutes in the patient with typical (normal) pseudocholinesterase enzyme.

This situation is not analogous to that in which the block is thought to shift from "depolarizing" to "nondepolarizing." These patients are unusually sensitive to anticholinesterase agents; hence, early use of neostigmine would in fact accentuate the block. Indeed, our first case revealed no shift in type of block when tested electronically, and the use of neostigmine would only have prolonged his problem.

Kalow noted that the abnormal or atypical pseudocholinesterase could be distinguished from the normal enzyme by comparing the degree of inhibition of dibucaine under controlled conditions. Typical (or normal) pseudocholinesterase activity is inhibited approximately 80% by dibucaine; atypical (or abnormal) pseudocholinesterase is inhibited approximately 20% by dibucaine, while some patient samples fall between the two extremes.

For more detailed understanding of the additional genetic variations and the diagnostic technics for identifying these variants, the reader is referred to the reports of Harris,[6,7] Neitlick,[8] Prince,[9] and Kalow.[10]

Of clinical importance is the diminished catabolism of other cholinesterase inhibitors experienced by patients with homozygous atypical pseudocholinesterase. They are at great risk from many organic insecticides as well as from procaine, physostigmine, ecothiopate iodide (eye drops),[11] hexamethonium fluoride, diisopropyl flurophosphate, and related compounds.

The point has been raised that since alkaline hydrolysis is an alternative route in

the degradation of succinylcholine, the administration of bicarbonate should be of value in terminating prolonged apnea. Since the problem is relegated primarily to the succinylcholine at the myoneural junction, the amount of IV bicarbonate required would probably have to be extremely large, creating additional problems for the patient. Kalow[10] points out that less than 5%/hr of succinylcholine present will be deactivated by alkaline hydrolysis. He writes:

"Interest in the subject has been initiated by the special medical and legal problems that arise when a hereditary defect causes a patient to be harmed by a conventional application of a conventional drug."

It would appear incumbent on anesthesiologists to document carefully all cases of prolonged apnea following single intubating doses of succinylcholine, to rule out the inherited metabolic defect. Only then can patients receive intelligent instructions regarding future operations and anesthesia. Fortunately, anesthesiologists have alternative drugs (nondepolarizers) and technics, so that succinylcholine can be avoided where circumstances require.

ACKNOWLEDGMENT

The authors are indebted to George Manners, PhD, head of the Anesthesia Research Laboratory of Dr. Francis Foldes, Montefiore Hospital and Medical Center, Bronx, New York, for the biochemical determinations.

REFERENCES

1. Bourne JG, Collier HO, Somers CF: Succinylcholine muscle relaxant of short action. Lancet 1: 1225-1229, 1952

2. Smith DL, Virtue RW: Succinylcholine: a case report. Anesthesiology 15:42-50, 1954

3. Borders RW, Stephen CR, Nowill WK, et al: The interrelationships of succinylcholine and the blood cholinesterases during anesthesia. Anesthesiology 16:401-422, 1955

4. Foldes FF, Swerdlow M, Lipschitz E, et al: Comparison of the respiratory effects of suxamethonium and suxethonium in man. Anesthesiology 17:559-568, 1956

5. Kalow W: Muscle relaxants. Anesthesiology 20:505-518, 1959

6. Harris H, Whittaker M: Differential inhibition of human serum cholinesterase with fluoride: recognition of two new phenotypes. Nature 191: 496-498, 1961

7. Harris H, Robson EB, Glen-Bott AM, et al: Evidence for non-allelism between genes affecting human serum cholinesterase. Nature 200:1185-1187, 1963

8. Neitlick HW: Increased plasma cholinesterase activity and succinylcholine resistance: a genetic variant. J Clin Invest 45:380-387, 1966

9. Prince LC, Garry PJ, Lubin AH: Silent cholinesterase gene—report of a family. Anesthesiology 37:652-653, 1972

10. Kalow W: Pharmacogenetics and anesthesia. Anesthesiology 25:377-387, 1964

11. Pantuck EJ: Ecothiopate iodide eye drops and prolonged response to suxamethonium. Br J Anaesth 38:406-407, 1966

NEW SMOKING MATERIAL The acute effects on airway function from smoking 1 cigarette made with either a tobacco substitute (cellulose base), 30% substitute/70% tobacco or conventional tobacco was determined in healthy nonsmokers and smokers. None of the three cigarettes produced changes in tests of small airway function. Constriction of large airways, as reflected by airway conductance, was produced by the conventional and 30/70 cigarette but not the substitute. The absence of large airway constriction probably results from the lower concentrations of particulate matter in the smoke of the substitute cigarette. Nevertheless, the 30/70 cigarette, which is the proportion likely to be used commercially, was not distinguishable from a tobacco cigarette. *(Costello JF, Douglas NJ, Sudlow MF et al: Acute effects of smoking tobacco and a tobacco substitute on lung function in man. Lancet 2:678-680, 1975)*

Anesthetic Considerations in Patients with Gas Gangrene

MICHAEL J. LAFLIN, LT*
RAYMOND E. TOBEY, CAPT†
J. G. REVES, LCDR‡

Anesthesia for a patient with gas gangrene presents a challenge for the anesthesiologist, since it is an uncommon disease requiring emergency treatment. The authors, faced with such a challenge and finding little guidance in the literature, have proposed modalities of anesthetic management based on pathophysiology, symptomatology, and the reported experience of others. In addition to choice of anesthetic agents, problems reviewed include shock, hypovolemia, tachycardia, fever, anemia, renal dysfunction, pulmonary insufficiency, and contamination. Factors relating to anesthesia during hyperbaric-O_2 therapy are also reviewed.

CLOSTRIDIAL myonecrosis, commonly referred to as gas gangrene, is a serious anaerobic infection. Fortunately, cases occur infrequently, but this may cause unsuspecting physicians to miss the early signs of the disease. Untreated, gas gangrene is uniformly fatal,[1,2] and even prompt and appropriate treatment does not insure survival. Debridement is necessary in most cases and anesthesia is almost always required during this portion of the therapy.

Recently, we were presented with the challenge of administering anesthesia to a severely ill patient with gas gangrene and failed to find any guidance in the literature to help us in our choice and management of anesthesia.[3-7] This prompted us to review the disease process in relation to anesthetic considerations.

DISCUSSION

In order to manage patients with serious physiologic derangements produced by an infecting organism, it is best to be aware of the disease process and, particularly, its alterations of organ systems affected during the course of anesthesia.

Incidence and Mortality.—Although most cases of gas gangrene occur in war casualties, it can follow the trauma of both accidents and surgery. The overall incidence of the disease is unknown. However, in the metropolitan area of Denver, Colorado (population, 1.4 million), for example, there are 3 to 5 cases per year.[8]

Overall mortality with different modalities of treatment ranges from 6.7 to 23%.[4,9] When the infection occurs following surgical procedures, the mortality rate is 33 to 45%, whereas in the case of accidental trauma, it is 10 to 12%.[10,11] This difference has been attributed to the higher index of suspicion in cases of accident compared to hospital-acquired infections.

Types of Infection.—Clostridial infection in man presents a wide spectrum of severity. MacLennan,[6] on the basis of his experience in World War II, has differentiated 3 types of infection on clinical grounds: simple contamination; anaerobic cellulitis; and anae-

*Resident, Department of Anesthesiology, National Naval Medical Center, Bethesda, Maryland 20014.

†Director, Division of Experimental Anesthesiology and Pharmacology, Naval Medical Research Institute, Bethesda.

‡Staff Anesthesiologist, Department of Anesthesiology, National Naval Medical Center.

The following represents the personal opinions of the authors and should not be considered as representing the official opinions of the Department of the Navy or the Department of Defense.

Paper received: 6/2/75
Accepted for publication: 10/1/75

robic myositis (clostridial myonecrosis or gas gangrene); of these, only gas gangrene is fatal.

PATHOPHYSIOLOGY

Organisms. — Six *Clostridia* species are capable of producing gas gangrene in man; *C perfringens* (also known as "Welch's bacillus") is the most common causative organism.[1]

Conditions for Infection.—*Clostridia* are found throughout nature and are protected from the lethal effects of ambient O_2 by spore formation. The spores are resistant to most methods of antisepsis but povidone-iodine compresses have been effective in reducing the numbers of skin contaminants.[12] Once *Clostridia* have been introduced into previously healthy tissue, specific alterations in the environment leading to a lowered oxidation-reduction potential must take place before multiplication of organisms can occur. These changes most commonly result from local ischemia.

The incubation period is variable; the average for *C perfringens* is 12 to 24 hours, but incubation periods as short as 1 hour and as long as 6 weeks have been reported.[1,13]

Toxins. — Once conditions suitable for multiplication are met, the increasing numbers of *Clostridia* release powerful exotoxins into adjacent tissues which kill viable cells, turning a benign infection into a potentially fatal disease. At least 12 such exotoxins have been identified from C perfringens[1] of which alpha toxin, a lecithinase, is the primary cytotoxic agent. It diffuses into surrounding healthy tissues where it attacks the lecithin component of cell membranes, causing disruption and lysis of the cells.[1] The *Clostridia* then migrate into these now necrotic areas, release more toxins, and continue their spread in geometric progression.

The other toxins appear to serve as spreading agents for the alpha toxin and as protectors of the infecting organisms from the body's defense mechanisms.

There is no clear understanding of the nature of the systemic toxemia, of the agents that cause it, or of the ultimate cause of death.

Local Effects.—These are the result of the rapidly spreading inflammatory process. The organisms liberate a gas which causes swelling, leading to vascular compression and further spread of the bacteria. The alpha toxin produces destruction and necrosis of muscle and also affects the integrity of capillary endothelial membranes, allowing transudation of fluid and edema formation.

SYSTEMIC EFFECTS

Hematologic. — Intravascular hemolysis and anemia occur with clostridial septicemia, most commonly with postabortal uterine myonecrosis,[1,14] hemolysis apparently resulting from intravascular production of alpha toxin.[1] Subsequent hepatic metabolism of the released hemoglobin leads to hyperbilirubinemia.

Cardiovascular.—The massive edema associated with the local wound, increased insensible loss from fever, and decreased oral intake produce hypovolemia. The common sign of tachycardia is secondary to hypovolemia, hemolytic anemia, fever, and toxemia. Blood pressure early in the course of the disease is normal or slightly elevated, but may fall precipitously to systolic levels of 80 torr or less as the disease progresses.[12] The etiology of the sudden hypotension is unclear.

Renal. — Renal dysfunction and failure occurred in 16% of Roding's patients with gas gangrene; 7.7% of the patients were anuric.[11] The dysfunction most likely occurs as a consequence of hemoglobinemia and hypotension. A circulating nephrotoxin produced by the action of clostridial toxins on uterine muscle has also been postulated.[14]

Thermal.—Temperature changes are variable but generally elevated with an average temperature of 38.3 C (36.1 to 41.7 C) in one series.[10]

TREATMENT

The mainstay of therapy remains debridement, even though other factors have modified the extent of the surgical procedures needed. It is during this phase of therapy that the anesthesiologist becomes involved with the patient and his disease. Since even small areas of involved muscle remaining after debridement may result in death, extensive debridement of all involved areas, including high amputation, has been recommended.[1,9,10]

Adjunctive modes of therapy include massive doses of aqueous penicillin G or tetracycline.[8,9] Some authors suggest that large doses of steroids may be beneficial in cases where the patient is in shock, but there are

no objective data to support this regimen.[8,9,15]

Considerable enthusiasm and controversy have accompanied the use of hyperbaric-O_2 (HBO) therapy. Since the initial encouraging report by Brummelkamp and associates[16] in 1961, many others have used such therapy with success. This therapy does not diminish the mortality rate of the disease but does diminish the degree of debridement required and allows some patients to avoid surgery altogether.[11] Many patients considered inoperable due to extension of the disease onto the trunk have been cured following HBO treatment.[9]

ANESTHETIC MANAGEMENT

Clinical problems of most concern to the anesthesiologist include shock, hypovolemia, tachycardia, fever, anemia, renal dysfunction, pulmonary insufficiency, and the local wound. In addition to these considerations, rapid recovery from the anesthetic is of practical importance, since patients for whom HBO therapy is used must be transported to the chamber for subsequent treatments. The ability of a patient to cooperate during a "dive" would lessen the risk of barotrauma. Another consideration is the requirement for multiple anesthetics during the management of wound closure and skin grafting in patients requiring extensive debridement.

Preanesthetic Assessment.—The most important aspect of the patient's status is the adequacy of his circulating blood volume. Besides noting the usual signs of pulse rate, blood pressure, and central venous pressure, the "tilt test" is a useful, quick, and simple test to help in one's judgment.[17] Fluid input and output changes are so rapid that radioisotope blood volumes are not helpful.

Evaluation of hematocrit is important, since hemolytic anemia may be a preoperative problem. Serum bilirubin, plasma hemoglobin, and CO levels are useful in assessing the patient's hematologic system. The CO level closely reflects changes in hemolytic rates, since it is one of the end-products of hemoglobin metabolism in a stoichiometric ratio.[18,19] Either whole or packed red blood cells should be matched in a volume adequate for replacement of anticipated losses, which in some cases may be large.

Fever is another complicating problem for the anesthesiologist. Antipyretics, cold fluids, and a cooling mattress are indicated in attempting to reduce the elevated temperature. However, operation should not be delayed in an attempt to reduce the temperature.

Monitoring. — Intraoperative monitoring consists of the usual devices employed in poor-risk patients. Esophageal stethoscope, temperature probe, ECG, central venous pressure line, and urinary bladder catheter are essential. In addition, a Swan-Ganz pulmonary-artery catheter and a peripheral artery catheter may be useful in the operative assessment of left heart function and adequacy of ventilation.

Induction.—Patients with gas gangrene often have full stomachs, and anesthesia must be induced with appropriate assurance of a patent airway and precautions against pulmonary aspiration of gastric contents.

Induction agents should be chosen on the basis of the patient's clinical condition. Sodium thiopental should be used with caution in hypovolemic patients, since rapid infusion may lead to hypotension.[20-22] Cardiovascular collapse may occur precipitously in patients with gas gangrene as a component of the disease process, and in these cases ketamine might prove a better choice, particularly when rapid induction of anesthesia is desired. Ketamine has been used successfully in some poor-risk hypovolemic patients;[22] however, its use in gas gangrene has not been studied.

Succinylcholine may be used for rapid muscle paralysis. The anesthesiologist, however, should be aware of the possibility of hyperkalemia and cardiac arrest when succinylcholine is used in the presence of other injuries, such as massive trauma, neurologic injury, or burns, not related to the site of clostridial infection.[23-27] Recent evidence indicates that excessive potassium release may occur as early as 3 to 4 days after injury,[28] which is often within the period of incubation and manifestation of gas gangrene. On the other hand, the large areas of necrotic muscle produced by the infection are relatively isolated from the circulatory system because of the vascular compromise characteristic of the disease, and are unlikely to represent a source of excessive K^+ release.

In cases where rapid muscle paralysis for endotracheal intubation is not necessary, a nondepolarizing muscle relaxant may be used. Pancuronium bromide has been shown to produce adequate relaxation for intubation in 2 to 3 minutes,[29] while supporting the blood pressure and pulse.[30,31] Awake

endotracheal intubation offers an alternative approach.

Maintenance.—The agents of choice for maintenance of anesthesia are not known because of lack of data. We chose halothane because it provides smooth anesthesia with rapid elimination and changes in depth, and can be used with high concentrations of oxygen. Its primary drawback is myocardial depression, but it may also be implicated in the event of jaundice, which occurs in 25% of cases of gas gangrene.[11]

The use of N_2O poses theoretic disadvantages, since it is known to expand air-containing spaces within the body by more rapid diffusion than outflowing nitrogen.[32,33] What effect this property might have on the gas pockets produced by the clostridial infection is speculative. While the "gas" of gas gangrene is primarily H_2, CO_2 is also produced; however, the latter is more soluble and, at least initially, readily absorbed into body fluids.[34]

A natural diffusion barrier to accumulation of N_2O in the tissues is provided by the areas of hypovascular and avascular muscle in which the gas is contained. Since the liberation of toxins has not been inhibited by *in vitro* O_2 exposures of less than 2.5 atmospheres,[35] there is no apparent advantage to the use of high O_2 concentrations. Whether the small pockets of H_2 liberated during debridement represent a fire hazard in the presence of electrocautery is unknown.

Balanced anesthesia or neuroleptanesthesia may be employed, the primary advantage being postoperative analgesia. However, it is important to have a rapid recovery from the anesthetic, since a cooperative patient is easier to manage in the hyperbaric chamber to which the patient may be immediately discharged for postoperative treatment.

Ketamine may be used as the sole agent in conjunction with 100% O_2, but the amount of drug required during a prolonged procedure could delay emergence. Also, an increase in the already elevated heart rate might increase myocardial O_2 demand in a heart with reduced reserves.

Nondepolarizing muscle relaxants are useful and should be selected according to clinical needs. Pancuronium and gallamine are indicated in hypovolemic patients but may increase an already elevated heart rate. Because of the potential development of renal failure, gallamine should be used judiciously. Curare should also be used cautiously because of its potential for producing hypotension. A need for postoperative ventilatory support with inadequate reversal of relaxants could be a serious problem, if the patient is to be transported to a hyperbaric chamber with limited access to the patient and little space available for a ventilator.

Spinal and epidural anesthesia are not recommended because of the unstable cardiovascular status. The possibility of introducing infection should also be considered. A brachial plexus block may be acceptable in the case of disease limited to the upper extremity, but one must bear in mind that a hematoma following the axillary approach could compromise vascular supply to tissue which already has only a marginal perfusion and O_2 supply. It may also be difficult to assess the proximal spread of the infection in deep muscle planes, and the tissues of the axilla may be involved.

As in all major surgical procedures, adequate crystalloid, colloid, and blood-component therapy is imperative. Such clinical signs as pulmonary capillary wedge pressure, central venous pressure, and urine output are useful in judging the adequacy of volume replacement.

CONTAMINATION

The final concern in anesthetic management is the problem of a patient with an infected wound. *C perfringens* species rarely form spores during active infection and, being obligate anaerobes, any vegetive organisms exposed to air should be rapidly neutralized.[36] The *Clostridia* species causing gas gangrene are only opportunistic pathogens,[37] and are not highly invasive except under conditions leading to a lowered oxidation-reduction potential.[36] Since the conditions suitable for infection occur only rarely,[37] cross-infection is unlikely.

MacLennan[6] found that only 1.5% of war wounds contaminated with *Clostridia* developed gas gangrene. When 2 cases of gas gangrene occurred within a 2-day period in 1 hospital, an epidemiologic study showed no relation between the 2 causative organisms.[12] The study further confirmed the widespread distribution of *Clostridia* spores. They are frequently found as a result of fecal contamination, but are also found in soil, dust,[34] clothing,[1] and even in low numbers in operating rooms.[12]

Thus, the rarity of spore formation, the ubiquitous nature of the organism, and the stringent conditions required for infection make isolation of patients unnecessary. The most effective means of sterilization of anesthesia equipment is steam autoclaving, but this, also, is probably unnecessary and in many instances impractical.

REFERENCES

1. MacLennan JD: The histotoxic clostridial infections of man. Bacteriol Rev 26:176-276, 1962

2. MacFarlane MG: The therapeutic value of gas gangrene antitoxin. Br Med J 2:636-640, 1943

3. DeHaven JE, Evarts CM: The continuing problem of gas gangrene: a review and report of illustrative cases. J Trauma 11:983-991, 1971

4. Pappas AM, Filler RM, Erkalis AJ, et al: Clostridial infection. Clin Orthop 76:177-183, 1971

5. Trippel OH, Ruggie AN, Staley CJ, et al: Hyperbaric oxygenation in the management of gas gangrene. Surg Clin North Am 47:17-27, 1967

6. MacLennan JD: Anaerobic infections of war wounds. Lancet 2:63-66; 2:94-99; 2:123-126, 1943

7. Erkalis AJ, Filler RM, Pappas AM, et al: Evaluation of hyperbaric oxygen as an adjunct in the treatment of anaerobic infections. Am J Surg 117:485-491, 1969

8. Weston EL, Kukral AJ: *Clostridia.* Rocky Mt. Med J 70:43-46, 1973

9. Altemeir WA, Fullen WD: Prevention and treatment of gas gangrene. JAMA 217:806-813, 1971

10. Altemeir WA: Diagnosis, classification, and general management of gas-producing infections, particularly those produced by *Clostridium perfringens,* Proceedings of the Third International Conference of Hyperbaric Medicine. Edited by IW Brown Jr. Washington DC, National Academy of Sciences, National Research Council, 1966, pp 481-490

11. Roding B, Groeneveld PHA, Boerema I: Ten years of experience in the treatment of gas gangrene with hyperbaric oxygen. Surg Gynecol Obstet 134: 579-595, 1972

12. Ayliffe GAJ, Lowbury EJL: Sources of gas gangrene in the hospital. Br Med J 2:333-337, 1969

13. Martin BP: A case illustrating the early onset of gas gangrene. J R Nav Med Serv 28:388-389, 1942

14. O'Neill JP, Niall JF, O'Sullivan EF: Severe postabortal *Clostridium welchii* infection: trends in management, Aust NZ J Obstet Gynaecol 12:157-165, 1972

15. Brummelkamp WH: Considerations of hyperbaric oxygen therapy at three atmospheres absolute for clostridial infections type welchii. Ann NY Acad Sci 117:688-689, 1965

16. Brummelkamp WH, Hogendijk J, Boerema I: Treatment of anaerobic infections by drenching the tissues with oxygen under high atmospheric pressure. Surgery 49:299-302, 1961

17. Green DM, Metheny D: The estimation of acute blood loss by the tilt test. Surg Gynecol Obstet 84:1045-1050, 1947

18. Sodeman WA Jr, Sodeman WA: Pathologic Physiology. Philadelphia, WB Saunders Company, 1974, p 579

19. Landau SA, Callahan EW Jr, Schmid R: Catabolism of heme *in vivo:* comparison of the simultaneous production of bilirubin and carbon monoxide. J Clin Invest 49:914-925, 1970

20. Van Bergen F: Clinical management of the patient in shock: nitrous oxide-thiopental-relaxant. Clin Anesth 2:1-23, 1965

21. Brown JM: Anesthesia and the contractile force of the heart: a review. Anesth & Analg 39: 487-498, 1960

22. Corssen G, Reves JG, Carter JR: Neuroleptanesthesia, dissociative anesthesia, and hemorrhage. Int Anesthesiol Clin 12:145-161, 1974

23. Birch AA, Mitchell GD, Playford GA, et al: Changes in serum potassium response to succinylcholine following trauma. JAMA 210:490-493, 1969

24. Tobey RE: Paraplegia, succinylcholine and cardiac arrest. Anesthesiology 32:358-364, 1970

25. Tobey RE, Jacobsen PM, Kahle CT, et al: The serum potassium response to muscle relaxants in neural injury. Anesthesiology 37:332-337, 1972

26. Schaner PJ, Brown RL, Kirksey TD, et al: Succinylcholine-induced hyperkalemia in burned patients—1. Anesth & Analg 48:764-770, 1969

27. Gronert GA, Theye RA: Pathophysiology of hyperkalemia induced by succinylcholine. Anesthesiology 43:89-99, 1975

28. John DA, Tobey RE, Rice CL, et al: Onset of succinylcholine-induced hyperkalemia following denervation. Abstracts of Scientific Papers, Annual Meeting of the American Society of Anesthesiologists, 1974

29. Katz RL: Clinical neuromuscular pharmacology of pancuronium. Anesthesiology 34:550-556, 1971

30. McIntyre JWR, Gain EA: Initial experience during the clinical use of pancuronium bromide. Anesth & Analg 50:813-823, 1971

31. Loh L: The cardiovascular effects of pancuronium bromide. Anaesthesia 25:356-363, 1970

32. Eger EI II, Saidman LJ: Hazards of nitrous oxide anesthesia in bowel obstruction and pneumothorax. Anesthesiology 26:61-66, 1965

33. Saidman LJ, Eger EI II: Change in cerebrospinal fluid pressure during pneumoencephalography under nitrous oxide anesthesia. Anesthesiology 26:67-72, 1965

34. Davis BD, Dulbecco R, Eisen HN, et al: Energy production, Microbiology. Second edition. Hagerstown, Maryland, Harper and Row, 1973, p 45

35. Van Unnik AJM: Inhibition of toxin production in *Clostridium perfringens in vitro* by hyperbaric oxygen. Antonie van Leeuwenhoek 31:181-186, 1965

36. Davis DB, Dulbecco R, Eisen HN, et al: General properties of the Clostridia, Microbiology.

Second edition. Hagerstown, Maryland, Harper and Row, 1973, pp 830-841

37. Smith LD, Dowell VR: *Clostridium*, Manual of Clinical Microbiology. Second edition. Washington DC, American Society for Microbiology, 1975, p 379

Guest Discussion

G. DOUGLAS BLENKARN, MD
Department of Anesthesia
Duke University Medical Center
Durham, North Carolina

Dr. Laflin's study presents the common combination in clinical gas gangrene: the ubiquitous presence of the seed (the clostridial spore) and the appropriate culture media (hypoxic tissue). The prerequisites of proper anesthetic management of these patients are identical to those of any critically-ill septic patient and include confirmation homeostasis of gas exchange by intermittent arterial blood-gas analysis and continuous direct monitoring of ECG, arterial and central venous pressure, and urine output.

Anesthetic agents selected are of less importance than the manner in which they are employed. We feel that anesthesia should be sufficiently light so as not to compromise cardiovascular reactivity. Accordingly, we would almost always select a narcotic-muscle relaxant technic, with supplementation by a volatile inhalation agent only if oxygenation was impaired.

It is now widely felt that the initial 3 hyperbaric-O_2 (HBO) treatments during the initial 24 hours are the most crucial. Whether surgical debridement or HBO is employed first after the presumptive diagnosis is reached depends upon the logistics of the situation. Ideally, all therapeutic modalities should be employed in every case of gas gangrene. If appropriate hyperbaric facilities and expertise are close at hand, and if the same standard of intensive care can be provided within the chamber, then no impediment exists to using this important adjuvant therapeutic modality.

Decompression sickness is never a problem for the patient, as he breathes close to 100% O_2. Difficulty in equilibrating the middle ear with the chamber pressure (barotrauma) is readily prevented by prophylactic myringotomy immediately upon recognition of any problem during the initial hyperoxic exposure.

During HBO treatment, it is essential to ensure delivery of close to 100% O_2 as the inspired gas and to confirm the expected degree of hyperoxemia by arterial blood-gas analysis performed within the chamber. As a significant physiologic shunt is present in almost all these patients, the theoretic high O_2 tensions (in excess of 1800 torr) are rarely achieved. A Pao_2 of greater than 1000, however, is acceptable while breathing 3 atmospheres of O_2 and hyperoxygenates perfusing tissues at the advancing edge of the infection, helping to arrest the vicious cycle of tissue death described by Dr. Laflin.

Central nervous system hyperoxic toxicity, as manifested by a general convulsion, is not uncommon. It can be minimized by appropriate sedation, treating hyperpyrexia, planned midway interruption of each HBO treatment with 5 minutes of air breathing, and by being alert to the appearance of any preconvulsive symptoms or signs, such as abnormal acuteness of hearing, nausea, or focal twitching.

However, if the logistics are such that HBO therapy significantly compromises any of the other modalities of therapy, one should forego HBO treatment.

Two other aspects of oxygenation deserve emphasis. Large amounts of blood are frequently required to replace that lost due to hemolysis and during and following surgical procedures. Also, the adequacy of oxygenation must be assured in the intervals between HBO exposures. Indeed, every patient should receive supplemental O_2 continuously until the infection is well under control and arterial oxygenation is adequate while breathing air.

Unfortunately, the general reaction of hospital personnel to patients with gas gangrene is analogous to their reaction to patients with venereal disease, so that gas-gangrene patients are not only isolated from other surgical patients but are frequently excluded from first-class intensive care by being sequestered in small isolation rooms.

REFERENCES

1. Blenkarn GD: Hyperbaric therapy: report of its utilization at the Toronto General Hospital. Can Med Assoc J 102:951-956, 1970

2. Holland JA, Hill GB, Wolfe WG, et al: Experimental and clinical experience with hyperbaric oxygen in the treatment of clostridial myonecrosis. Surgery 71:75-85, 1975

Theoretic Significance of pH Dependence of Narcotics and Narcotic Antagonists in Clinical Anesthesia

DONALD W. BENSON, MD, PhD*
JOYCE J. KAUFMAN, PhD†
WALTER S. KOSKI, PhD‡
Baltimore, Maryland§

Determination of the effect of pH and temperature on pK_a partition, and drug distribution coefficients in a series of common narcotics and their antagonists has shown that within the range of blood pH (7.1 to 7.7) encountered in the practice of anesthesiology, marked differences of distribution of the drugs between a model lipid (octanol) and water can occur. When these data are considered in the light of clinical experience with narcotics used in patients undergoing or recovering from surgical procedures, a correlation between the depth and duration of narcosis or the efficacy of narcotic antidotes and ventilatory status is seen. This correlation can be explained in part if the influence of blood pH on the probable CNS/blood distribution of a given drug is taken into consideration. Support is given to this proposal by representative studies in the literature. The very different drug distribution coefficients of two closely related narcotic antagonists, naloxone and naltrexone, correctly predicted the faster onset and shorter duration of the former, which was confirmed by reported clinical observations.

WE RECENTLY measured, by microelectrometric titration,[1,2] pK_a‖ and partition coefficients, and drug distribution coefficients between octanol and water as a function of pH and temperature[3-6] in a number of clinically used narcotics and narcotic antagonists. The partition coefficients and drug distribution values at 37° C are higher than those at 20° C,[6] the temperature at which such measurements have usually been made. There are significant nonuniform increases in the drug distribution coefficients between 20° and 37° C, ranging from 21% for morphine to 200% for naltrexone.

The nonregularity of increase with temperature emphasizes the necessity for measurements at 37° C, since our study[6] showed that extrapolation of measurements made at lower temperatures to body temperature by any constant factor is not valid. Partition coefficients (P) refer to the partitioning of the same species, in this case the free base, between oil and water. Drug distribution coefficients $P_{apparent}$ (P_a) (or apparent partition coefficients), refer to the distribution

‖pK_a: The negative logarithm of an apparent ionization constant, K′. The buffering power of a buffer system is highest when pK′ = pH.

*Professor and Chairman, Department of Anesthesiology, University of Chicago Hospitals, Chicago, Illinois 60637.

†Associate Professor, Department of Anesthesiology, and Principal Research Scientist, Department of Chemistry, The Johns Hopkins University, 21218.

‡B. N. Baker Professor, Department of Chemistry, The Johns Hopkins University, 21218.

§Department of Anesthesiology, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205.

This study was supported in part by grant DA00539 from NIDA, Biomedical Branch, Division of Research.

Reprint requests to Dr. Kaufman.

Paper received: 10/24/74
Accepted for publication: 6/25/75

$$P_a = \frac{[\text{free base} + \text{acid salt}]_{\text{lipid}}}{[\text{free base} + \text{acid salt}]_{\text{water}}} \simeq \frac{[\text{free base}]_{\text{lipid}}}{[\text{free base} + \text{acid salt}]_{\text{water}}}$$

(since essentially it is only the free base which partitions into the lipid).

These drug distribution coefficients are related to the amount of drug that will pass the blood-brain barrier and enter the CNS, and are the pharmacologically significant quantities when considering drug dosages. Reporting our data as P or P_a rather than as the more customary, less sensitive, log P, enables clinically significant differences to be ascertained. The narcotics investigated included morphine, codeine, oxymorphone, levorphanol, meperidine (pethidine), methadone, and alpha acetylmethadol (a derivative of methadone with a longer duration of narcotic action, being tested clinically in experimental drug addiction). (It should be noted that the narcotic properties of codeine occur as a result of its demethylation.) The narcotic antagonists investigated included nalorphine (a mixed agonist-antagonist), naloxone, naltrexone (the N-cyclopropylmethyl derivative of oxymorphone), levallorphan, cyclazocine, and pentazocine (the two latter are classed as mixed agonist-antagonists).

METHODS

The microelectrometric titration apparatus used in this study is an adaptation of conventional assemblies. It consisted of a small thermostatted cell in which about 0.04 mM of sample was dissolved in 5 ml of CO_2-free triple-distilled water. A blanket of N_2 gas was maintained over the sample to prevent any absorption of CO_2 from the room atmosphere. pH measurements were made with a PHM64 radiometer pH meter with calomel-and-glass electrodes. A microburet coupled with a microdelivery tip permitted accurate additions of small quantities of titrant (2N NaOH). A magnetic stirrer was used for proper agitation.

In determining the pK_a, a conventional titration curve in which one plots volume of titrant versus pH is obtained. A blank titration curve prepared in the same manner, but without the sample, was subtracted from the first curve. This resultant curve has a shape represented by the following equation

$$pH = pK_a + \log\frac{\alpha}{1-\alpha}$$

The pH at which α, the fraction of sample in the dissociated state for acids or the associated state for bases was 0.5, was taken as the pK_a.

The distribution coefficient of the drug was determined by titrating the compound in a two-phase system (octanol and water). If a compound is added to such a two-phase system in an amount insufficient to saturate either of the phases, the material will distribute between the two phases in a definite proportion determined by its distribution coefficient (P). Octanol is used to simulate the lipid because of its wide use as standard in such applications.[7]

The compound dissociates into its respective ions in the aqueous phase. The extent of the dissociation is determined by the dissociation constant (K_a), which was obtained from the experimentally determined titration curve. When the drug is titrated in the presence of a finely dispersed oil, the free acid or base rapidly partitions between oil and water and, as the titration proceeds, the dissociation equilibrium in the aqueous phase continues to follow the relation

$$K_a' = \frac{[H^+]\,[A^-]}{[HA]}$$

for the acid (HA), and a corresponding relation applies when a base is used. The removal of HA into the oil results in a shift in the apparent pK_a by an amount which depends on the volumes of water and oil present (the shift occurs to higher pH if an acid is titrated and to lower pH if a base is titrated in the presence of the two-phase system). This shift can be simply related to the distribution coefficient (P) by the equation

$$P = \frac{V_w\ (\text{antilog}\ pK_a' - 1)}{V_o}$$

in which the volumes of water (V_w) and oil (V_o) are known. From the measured shift of pK_a' ($\triangle pK_a'$), the distribution coefficient can be calculated.

RESULTS AND DISCUSSION

The marked sensitivity of the drug distribution coefficients to pH in the range from 7.1 to 7.7 may have significant consequences in a variety of clinical situations. These data at 37° C, encompassing the physiologically significant pH range 7.1 to 7.7, are presented in the table.

We have observed* that surgical patients under narcotic analgesia (for example with meperidine) and concomitant N_2O-O_2 anesthesia, if hyperventilated during the course of the operation, exhibit a deeper plane of analgesia, almost as if they had been given larger doses of narcotic. The data in the

*Benson DW: Unpublished data.

TABLE

Drug Distribution Coefficients at 37° C as a Function of pH

	pK_a	P7.1	P7.35	P7.4	P7.45	P7.5	P7.6	P7.7
Morphine sulfate	7.93	0.80	1.30	1.42	1.54	1.68	1.98	2.30
Codeine phosphate	8.10	1.25	2.07	2.28	2.51	2.75	3.30	3.91
Nalorphine HCl	7.59	17.55	26.22	28.16	30.16	32.19	36.39	40.41
Oxymorphone HCl	8.17	0.53	0.89	0.98	1.08	1.19	1.43	1.71
Naloxone HCl	7.82	19.49	30.82	33.55	36.42	39.43	45.79	52.54
Naltrexone HCl	8.13	7.11	11.86	13.08	14.40	15.82	18.99	22.57
Meperidine HCl	8.50	20.20	34.87	38.82	43.17	47.96	58.99	72.17
Methadone HCl	9.26*	58.68	103.81	116.33	130.30	145.92	182.92	229.04
α-acetylmethadol HCl	8.61*	611.81	1063.02	1185.25	1321.03	1470.46	1817.45	2235.98
Levorphanol tartrate	9.36*	6.89	12.21	13.69	15.34	17.18	21.56	27.02
Levallorphan tartrate	8.50*	116.63	201.35	224.17	249.30	276.95	340.66	416.76
Cyclazocine	9.38*	10.86	19.21	21.54	24.14	27.05	33.94	42.55
Pentazocine	9.16*	55.99	98.89	110.76	124.00	138.81	173.79	217.29

*$pK_{a(H_2O)} = pK_{a(50\%\ EtOH - H_2O)} + 0.5$ pH.

The tabulated partition coefficients represent averages of at least 4 determinations in the range of 2 to 20% oil in water. As expected, precision was poorest in cases where pK_a shift was smallest. In such cases as morphine sulfate or oxymorphone HCl, maximum scatter was about 15% of the value listed. In other cases it was much smaller.

table show that the drug distribution coefficient of morphine is raised 62% when the pH of the aqueous phase is changed from 7.4 to 7.7. This rise in drug distribution coefficient will be exhibited to a greater or lesser extent by all narcotics having a protonated amine.

Thus, it seems appropriate for the anesthesiologist giving narcotics preoperatively or during an operation to consider the effect of hyperventilation during anesthesia. The almost threefold increase in the drug distribution coefficient of morphine between pH 7.1 and 7.7 indicates that possible respiratory and/or metabolic alkalosis or acidosis may have a considerable effect on the degree of narcosis achieved.

Use of naloxone to back-titrate patients given morphine was described recently.[8] Since naloxone also exhibits a marked 57% rise in drug distribution coefficient from pH 7.4 to 7.7 (and a marked 42% decrease from pH 7.4 to 7.1), it would appear that dosage might be pH-dependent as well as time-and-quantity dependent.

Another area where pH-dependent distribution of narcotics may be important is in obstetrics. The blood of an infant during parturition and shortly after birth is more acidic (~7.2) than that of the mother.[9] Thus, it would be expected that the blood levels of basic drugs would be higher in the infant than in the mother if placental transport occurred by rapid passive diffusion of the unionized drug.[10] The placental barrier is mainly lipoprotein in nature; therefore, lipophilic drugs can pass more easily. Once the free base (unionized) form of the drug has traversed the placental barrier from the mother to the fetus (which is governed by the lipid-water drug distribution coefficient), the lower the pK_a of the narcotic (or narcotic antagonist), the more it is apt to become concentrated in the fetus, since only the free base can retraverse the placental barrier.

In the study of Beckett's group,[10] cited above, pentazocine and meperidine were given both singly and in combination to parturients in labor. Pentazocine was found to have a lower concentration in the newborn than in the mother, whereas the concentrations of meperidine in the newborn were higher than those in the mother. Those authors suggested that meperidine traversed the placental barrier more rapidly than pentazocine.

Our data would suggest an alternative explanation. The drug distribution coefficients of pentazocine are considerably higher at all pH values than those for meperidine. The lower pH of the fetal blood compared to that of the mother resembles a two-compartment system. Some of the unchanged free base of both narcotics will be converted into the acidic form and thus be unable to traverse the barrier in the reverse direction. The pK_a of meperidine at 37° C (8.5 by direct titration in H_2O solution) is lower than that of pentazocine (9.16 extrapolated to 100% H_2O from titration in 50% EtOH-H_2O solution). Thus, the lower pH of the fetus would cause proportionately more meperidine than pentazocine to convert back to the protonated form, and as a result relatively more of the pentazocine than of the meperidine entering the fetus would be able to retraverse the placental barrier back to the mother.

The reversal effect of nalorphine or naloxone and their pH dependencies may also be especially important in obstetrics. Where heavy medication with narcotics is used during labor and a narcotic antagonist is given the infant, there is significant acidosis in depressed babies.[11-13] Our drug distribution data would suggest that nalorphine would be 20 to 25% less effective at pH values of 7.15 to 7.23, as noted in the cited studies, than at normal pH value of 7.4. Our data suggest that naloxone would probably pass into the CNS only marginally more effectively than nalorphine at these low pH values. However, the data further indicate that hyperventilation to a higher pH would make nalorphine a more effective antagonist, since the drug distribution coefficient is higher at higher pH values. For the same reason, hyperventilation would also increase the antagonist efficiency of the naloxone.

The drug distribution coefficient of naltrexone is significantly lower than that of naloxone, more than might have been expected from the similarity in their structures, with naltrexone being significantly less lipophilic than naloxone. We had postulated that this would lead naloxone to have a more rapid onset for antagonist activity and likewise a shorter duration of action than naltrexone.[4] Clinical studies confirmed this prediction.* The lower oil/water drug distribution coefficient of naltrexone might indicate a larger dosage of naltrexone than of naloxone to be necessary for effective antagonist activity.

*Kurland AA, Director, Maryland Psychiatric Research Center, Spring Grove Hospital, Baltimore, Maryland: Private communication, 1974.

ACKNOWLEDGMENT

We thank Drs. Monique Braude and Robert Willette, Biomedical Research Branch, NIDA, for their perceptiveness in visualizing the contributions such studies make.

REFERENCES

1. Parke TV, Davis WW: Use of apparent dissociation constants in qualitative organic analysis. Anal Chem 26:642-647, 1954

2. Davis WW, Kruetler CJ: ANAL 8: Electrometric titration procedure for determination of aqueous solubility or organic acids and bases and ANAL 9: Electrometric titration procedure for determination of the oil to water partition of organic acids and basis. Papers presented before the Division of Analytical Chemistry 164th National American Chemical Society Meeting, Washington, DC, September 1971

3. Kaufman JJ, Koski WS: Physicochemical, quantum chemical and other theoretical techniques for the understanding of the mechanism of action of CNS agents: psychoactive drugs, narcotics, antagonists and anesthetics. Drug Design V, 251-340, EJ Ariens, Editor, Academic Press (1975)

4. Kaufman JJ: Physicochemical and quantum chemical studies of narcotics and narcotic antagonists. Presented at the Drug Dependence Meeting Satellite Session, Cocoyoc, Mexico, March 1974

5. Kaufman JJ: Quantum chemistry — from molecular collisions to molecular medicine. Garvan Medal Award Address, 167th National American Chemical Society Meeting, Los Angeles, California, April 1974, abstract phys #3

6. Kaufman JJ, Semo NM, Koski WS: Microelectric titration measurement of the pK_a's and partition and drug distribution coefficients of narcotics and narcotic antagonists and their pH and temperature dependence. J Med Chem 18:647-655, 1975

7. Leo A, Hansch C, Elkins D: Partition coefficients and their uses. Chem Rev 71:525-616, 1971

8. Longnecker DE, Grazis PA, Eggers GWN Jr: Naloxone for antagonism of morphine-induced respiratory depression. Anesth & Analg 52:447-453, 1973

9. Low JA: Acid-base assessment of the fetus in the normal obstetric patient. Obstet Gynecol 22: 15-18, 1963

10. Beckett AH, Taylor JF: Blood concentrations of pethidine and pentazocine in mother and infant at time of birth. J Pharm Pharmacol 19:50S-52S, 1967

11. Rogers CD, Wickard CP, McCaskill MR: Labor and delivery without terminal anesthesia: a report on the use of chlorpromazine. Obstet Gynecol 17:92-95, 1961

12. Clarke RB, Cooper JO, Stephens SR, et al: Neonatal acid-base studies. II. Effect of a heavy medication-narcotic antagonist regimen for labor and delivery. Obstet Gynecol 33:31-34, 1969

13. Foldes FF, Montefiore Hospital and Medical Center, Bronx, New York (quoted in ref 11)

Management of Intractable Pain in Adiposis Dolorosa with Intravenous Administration of Lidocaine

TADASHI IWANE, MD*
MASANORI MARUYAMA, MD†
MICHIKO MATSUKI, MD‡
YUSUKE ITO, MD§
KOKI SHIMOJI, MD‖
Niigata, Japan**

Intractable pain in a patient with adiposis dolorosa (Dercum's disease) was treated by IV administration of lidocaine (200 to 400 mg). Relief was maximum 20 minutes after the end of drug infusion and persisted for over 10 hours. Toxicity was minimal. Slow EEG waves which appeared during drug administration disappeared within 20 minutes.

DERCUM[1] described 3 cases of adiposis dolorosa (Dercum's disease) as long ago as 1892, but the etiology of this condition is still unknown. Common characteristics of Dercum's disease have been described as follows:[2]

1. Painful diffuse fatty deposits except in the face, the backs of hands, and the insteps.

2. Postmenopausal women are most often affected.

3. Asthenia, weakness, and fatigue are marked.

4. Psychic phenomena, including neuroses and emotional instability, are common.

No successful treatment of the disease has yet been established, but partial relief of pain by IV administration of lidocaine appears of palliative value.

CASE REPORT

A 48-year-old woman was admitted to the Niigata University Hospital on October 14, 1974, with the chief complaint of intractable pain over the whole body which was exacerbated by touch or pressure.

In 1968 she was treated with dexamethasone for pain in the right hip joint. In October 1969, she underwent an operation on her right hip joint, following which edema of the lower extremities was treated with diuretics.

In May 1972, pain in all joints as well as butterfly-like erythema on the face appeared; this was diagnosed as systemic lupus erythematosus (SLE). At that time, fatty deposits appeared in the left forearm and her

*Instructor.
†Assistant Professor.
‡Assistant Professor.
§Associate Professor.
‖Professor.
**Department of Anesthesiology, Niigata University School of Medicine, Niigata, Japan.

Paper received: 4/9/75
Accepted for publication: 7/10/75

body weight increased, with pain due to pressure over her whole body.

In June 1973, she was examined at a university hospital and SLE was suspected. In February 1974, she experienced unconsciousness for about 30 minutes. Subsequently, her movements were accompanied by increased spontaneous pain, hyperalgesia, and thermohyperesthesia. Psychiatric and EEG examinations revealed that, although hysteria could not be ruled out, Dercum's disease was probable.

On November 20, 1974, the patient presented in a wheel chair. She was obese, weighing 66 kg at a height of 150 cm, with fat deposits general except on her face, hands, and insteps. Her entire body surface was painful to the touch. She complained that her right shoulder and hip joint were so painful that walking was difficult. She could bathe only in tepid water because of thermohyperesthesia, and complained of insomnia.

Lidocaine (200 mg) was administered IV over 35 minutes. Ten minutes after the start of administration, the patient developed a feeling of heat, flushing of the breasts, euphoria,[3] numbness, and appeared hypnotized. Blood-gases analyzed immediately after drug administration were within normal limits. The patient complained of a slight headache 10 minutes after the end of administration.

She is presently (April 1975) being treated on alternate days with 400 mg of IV lidocaine given over a 15-minute period. Maximum relief is observed about 20 minutes after drug administration and relief continues for over 10 hours. Pain relief in the distal region of the bilateral elbow joints is now marked, mobility of the thumbs and fingers is improved, and she walks more easily than previously. However, some pain in the right shoulder and hip joint has persisted.

DISCUSSION

Despite several reports on Dercum's disease, optimum analgesia has not yet been described. Tetraethylammonium chloride[4] and epidural or spinal anesthesia[5] have been tried but with only partial success. As Dercum found connective tissue infiltration around the nerves in fatty deposits, neuritis has been suspected as the cause of pain,[5] but this theory has not been confirmed.

Local IV anesthetics have been used for management of pain due to burns, cutaneous cicatrices, dermatomyositis, pruritus, and cardiac arrhythmias.[6,7] However, the mechanism of action of these agents has not been elucidated. Lidocaine may block impulse conduction in peripheral nerves[8] and depress cerebral activity,[9] which may result in increased pain threshold. Central effects of some local anesthetics have been reported to be biphasic,[9,10] a small dose having an anticonvulsive activity while a large dose may induce convulsions. Sakabe's group[9] found that small doses of lidocaine (3 to 15 mg/kg) depressed the cerebral metabolism dose-dependently, reflected by a decrease in cerebral metabolic rate of O_2 consumption and an inhibition of electrical activity of the brain.

In our patient, the EEG showed slow waves, which appeared in 7 minutes after the start of administration and disappeared within 20 minutes after the end of drug administration (fig 1). By contrast, the pain relieving effect was found to be maximum at about 20 minutes after the end of administration. This suggests that pain relief following the administration of lidocaine may not depend on depression of cerebral activity but on its effect on peripheral nerves. The ECG, blood pressure, pulse rate, and respiratory rate have shown no remarkable changes during or after lidocaine administration (fig 2).

Arthralgia, however, has been only slightly alleviated even by this treatment and ankylosis has kept the patient almost bedfast. Thus, while lidocaine administration has not effected a complete cure, it has at least provided substantial relief for the otherwise intolerable pain of Dercum's disease.

REFERENCES

1. Dercum FX: Adiposis dolorosa. Am J Med Sci 104:521-535, 1892

2. Cantu JM, Ruiz-Barquim E, Jimenez M, et al: Autosomal dominant inheritance in adiposis dolorosa (Dercum's disease). Humangenetik 18:89-91, 1973

3. Foldes FF, Molloy R, McNall PG, et al: Comparison of toxicity of intravenously given local anesthetics in man. JAMA 172:1493-1498, 1960

4. Striger WA, Litvin H, Lasche EM, et al: Adiposis dolorosa (Dercum's disease). N Engl J Med 247:393-396, 1952

5. Blomstrand R, Juhlin L, Nordenstam H, et al: Adiposis dolorosa associated with defects of

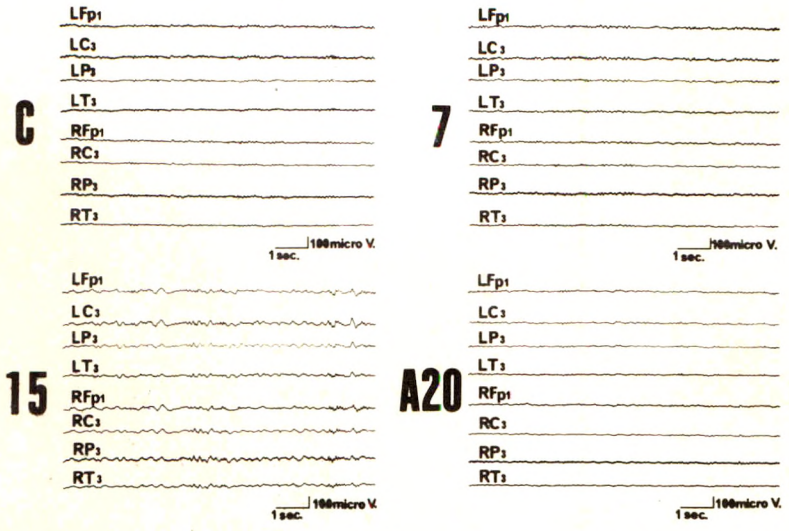


FIG 1. EEG changes before and after IV administration of lidocaine (400 mg). C: Control (before), and 7 and 15 minutes after start of administration; A20: 20 minutes after end of administration.

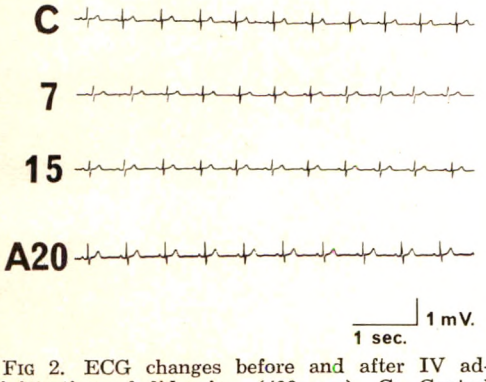


FIG 2. ECG changes before and after IV administration of lidocaine (400 mg). C: Control (before), and 7 and 15 minutes after start of administration; A20: 20 minutes after end of administration.

lipid metabolism. Acta Dermatover (Stockholm) 51:243-250, 1971

6. Bonica JJ: The Management of Pain. Philadelphia, Lea & Febiger, 1954, pp 1226-1261

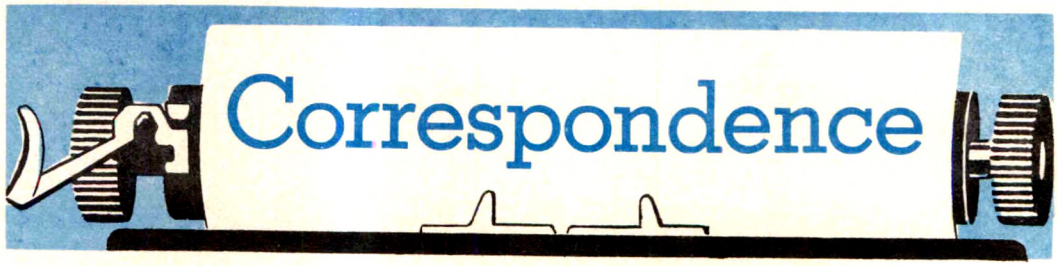
7. Grossman JI, Lubow LA, Friedem J, et al: Lidocaine in cardiac arrhythmias. Arch Intern Med 121:396-401, 1968

8. de Jong RH: Physiology and Pharmacology of Local Anesthesia. Springfield, Illinois, Charles C Thomas, Publisher, 1970, pp 140-142

9. Sakabe T, Maekawa T, Ishikawa T, et al: The effects of lidocaine on canine cerebral metabolism and circulation related to the electroencephalogram. Anesthesiology 40:433-441, 1974

10. Wagman IH, de Jong RH, Price DA: Effects of lidocaine on the central nervous system. Anesthesiology 28:155-172, 1967

PRACTOLOL The selective effects of low (1.5 mg/kg) and high (12 mg/kg) doses of oral practolol on beta-1 and beta-2 receptors was evaluated in 10 volunteers. Low doses of practolol produced 40 per cent blockade of the heart rate response to exercise but did not alter forearm vasodilator responses to isoproterenol. In contrast, the high doses produced blockade of both cardiac and vascular responses. The beta-1 blockade was not greatly different between the 2 doses. Thus, a low practolol dose blocks beta-1 responses but at higher doses this selectivity is lost as beta-2 responses are also blocked without any additional blockade of chronotropic responses. *(Lertora JLL, Mark AL, Johannsen UT et al: Selective beta-1 receptor blockade with oral practolol in man. A dose related phenomenon. J. Clin Invest 56:719-724, 1975)*



To the Editor:

I was interested to read the report by Orr,[1] describing the reversal by physostigmine of delirium induced by ingestion of the flowers of the plant *Datura stramonium*.

A member of this family of plants, *Datura arborea* (popularly known as "trumpet lily"), is widely distributed in this state, and earlier this year one of a group of 7 youths died after ingesting its flowers, the others developing a delirium lasting some 18 to 24 hours.

Based on the similarity between the symptoms of *Datura* poisoning and the central anticholinergic syndrome,[2] I suggested elsewhere at the time[3] that the centrally-active anticholinesterase, tetrahydroaminacrin (tacrine, THA) [Romotal®] would effectively reverse the symptoms and signs of such poisoning, as unfortunately physostigmine for parenteral use is not available in Victoria.

Orr's comment that further encounters with *Datura* can be anticipated appears relevant to both countries, and the availability of a specific antidote should be widely publicized.

George Mendelson, MD
Prince Henry's Hospital
Melbourne, Australia

REFERENCES

1. Orr R: Reversal of Datura stramonium delirium with physostigmine: report of three cases. Anesth Analg 54:158, 1975

2. Duvoisin RC, Katz R: Reversal of central anticholinergic syndrome in man by physostigmine. JAMA 206:1963, 1968

3. Mendelson G: Hallucinogenic plants (letter to editor) Med J Aust 1:839, 1975

Editor's comment: Unfortunately, no form of tetrahydroaminacrin is commercially available in the USA, although Romotal® can be found in most European countries.

Editors share the belief that medical writing is capable of vast improvement. This article is one of a series of personal communications from Charles G. Roland, M.D., former Senior Editor of JAMA, to John T. Martin, M.D., Associate Editor of Anesthesia & Analgesia . . . Current Researches. Dr. Roland is Chairman, Department of Biomedical Communications, Mayo Clinic, Rochester, Minnesota 55901.

Thoughts About Medical Writing

XXXIV. The Publication Process

Dear Tom:

The world of medical publication is a mystery to all but a few insiders. Of the whole population of physicians, relatively few write for publication. And of those who do, only a small fraction write often enough to become acquainted with the details of the process or to have a reason to be concerned with matters such as priority or publication ethics.

Part of the difficulty is that we know little about publication, in the scientific sense of knowing; the process itself has been little studied. The critical evaluation of the whole field, which can be termed the sociology of medical knowledge, is only beginning to be carried out.

Some examples are outstanding exceptions to this generality. For instance, Merton has studied multiple discoveries of the same fact or observation.[1] He has noted that it is not at all unusual for two or more investigators to make the same observation independently. This is a common phenomenon. Not only that, Merton has pointed out that disputes about priority are common and natural; he has found it almost a rule that a scientist who writes his biography and who claims to have no major concern for priority will, within a few pages, make such a claim. Or, as Merton put the thought in more general terms: "The expression of disinterested moral indignation is a signpost announcing the violation of a social norm."[2]

So it seems that it is normal to expect other investigators to be studying the phenomena that interest you. And it is just as normal for someone who has achieved priority to want public credit for it—and to seek out the credit, if necessary.

There are other "normalities" that fit into this study called the sociology of medical knowledge. Price, in one of the best known investigations in the field, brought to prominence the principle of doubling times for scientific knowledge. The number of scientific journals, for example, has doubled about every 15 years since journals first were published three centuries ago. An even more impressive extrapolation is Price's statement that "we can say that 80 to 90 percent of all the scientists that have ever lived are alive now."[3]

We are, then, beginning to know some facts about scientific knowledge itself. But, as in all fields of science, every casual assumption needs quantification and verification. In my opening paragraph I said that relatively few physicians write for publication. How few? Of those who write, is it true (as has been shown in other fields)

that only 10% of the writers write 90% of what is written? And if so, what does it mean? Someone needs to study those questions.

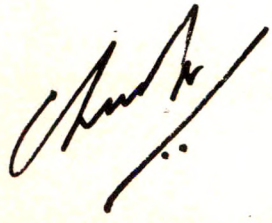
On a much smaller scale, we need to know more about the actual publication process itself. One recent study was devoted to 103 papers published from the Mayo Clinic. When these papers were categorized by type, it was found that both laboratory research papers and clinical research papers had an average span of over 4 years. That is, from the time the chief investigator had his or her idea to do a certain study, until the publication of the results of the study, took that long. For case reports it was more than 2 years and for review articles it was more than 3 years.[4]

This same study showed that journal handling times were not remarkably long, even though the impatient author may find this difficult to believe. The time lapse from submission of an article to its ultimate publication (85% of the papers being accepted by the journals to which they were first submitted) ranged from 25% to 30% of the total span.

Other data come from such investigations —some of it seemingly trivial. More than 80% of the authors write out their manuscripts longhand[4] (and so do I). One percent of these authors never revise their manuscripts; the first draft is good enough for them.

What does all this lead to? We know a little about the sociology of the way we acquire and distribute knowledge. We need to know much more. Simplistically, perhaps, we may come to believe that knowing more about the medical *writing* aspects of the process could help ease the task of the writer in some way; one fact is certain—most medical writers don't enjoy the writing itself. Yet I must admit a bias. I don't think that writing is supposed to be easy. Wasn't it Sheridan who said "Easy writing's curst hard reading"?

Regards,



[Charles G. Roland, M.D.]

REFERENCES

1. Merton RK: Singletons and Multiples in Science. Proc Amer Philosoph Society 105:470-486, 1961

2. Merton RK: Priorities in Scientific Discovery. Amer Sociol Rev 22:635-659, 1957

3. Price DJ de Solla: Little Science, Big Science. New York, Columbia University Press, 1963, p 1

4. Roland CG, Kirkpatrick RA: Time lapse between hypothesis and publication in the medical sciences. New Engl J Med 292:1273-1276, 1975

SILICONE CATHETERS Silicone elastomer intravenous catheters were used to provide total intravenous nutrition for an average 20.4 days (range 4 to 56 days). A crank introducer unit permitted the catheters to be introduced into the basilic or cephalic vein and then advanced into the superior vena cava. Thirty of 36 catheters were removed because they were no longer needed. Thrombophelbitis developed in 2 patients when the catheter tip was in the axillary vein and in 2 patients when the catheter had been inserted into previously punctured veins. Advantages of the silicone catheters are flexibility reducing the chances for vessel perforation or intima damage, minimal thrombogenicity, tissue compatibility and radiopacity. This approach offers an alternative to placing the catheter in the neck. *(Hoshal VL: Total intravenous nutrition with peripherally inserted silicone elastomer central venous catheters. Arch Surg 110:644-646, 1975)*

A Comparative Study of Enflurane and Halothane Using Systolic Time Intervals

JOEL A. KAPLAN, MD*
EDWARD D. MILLER, MAJ, MC†
DANIEL R. BAILEY, MAJ, MC‡

The effects of enflurane and halothane anesthesia on systolic time intervals were studied in 12 healthy patients. Cardiovascular measurements were made at equipotent levels of anesthesia: enflurane 1.23% end-tidal and halothane 0.65% end-tidal. These agents were studied first with 50% N_2O and then without N_2O. Systolic, diastolic, and mean arterial blood pressure were decreased more by enflurane than by halothane ($p<0.05$). However, halothane caused significantly more myocardial depression than enflurane, as indicated by a larger preejection period (PEP) and preejection period/left ventricular ejection time (PEP/LVET) and a smaller $1/PEP^2$ and ejection fraction. When N_2O was discontinued, both agents increased PEP and PEP/LVET and decreased $1/PEP^2$ and the ejection fraction.

WHEN administered in clinical doses, enflurane produces a stable cardiovascular system. Spontaneous arrhythmias are unusual except for an occasional nodal rhythm. Marshall and associates[1] showed, in 6 healthy patients, that during enflurane anesthesia (1 MAC), the cardiac index is only minimally reduced at normocarbia and hypocarbia, and is elevated at hypercarbia. Previously, Prys-Roberts and colleagues[2] had shown, in patients anesthetized with similar concentrations of halothane, that there is a marked reduction in cardiac index at all levels of CO_2. Bahlman's group[3] demonstrated that cardiac output decreased after 1 hour of halothane anesthesia but increased to levels above control at the end of 5 hours of anesthesia.

It is still unclear whether enflurane differs from halothane as a negative inotropic agent. *In-vitro* studies using cat papillary muscle have produced conflicting results. Studies by Shimosato and colleagues[4,5] on contractile parameters have shown halothane to be more of a depressant than enflurane, but a study by Brown and Crout[6] showed enflurane to be the most depressant of 5 general anesthetic agents. These *in-vitro* studies raise questions of differences in species, experimental design, and *in-vitro* versus *in-vivo* situations.

The measurement of systolic time intervals is a noninvasive technic that has been shown to correlate well with direct internal measurements of left ventricular function (LVF) in man.[7] Martin and coworkers,[7] studying 6 patients during cardiac catheterization, found identical values whether systolic time intervals were measured externally or internally. Following acute pharmacologic intervention, the preejection period (PEP) and left ventricular dp/dt correlated well and varied inversely.

*Assistant Professor of Anesthesia, Emory University School of Medicine; Director, Division of Cardiothoracic Anesthesia, Emory University Hospital, Atlanta, Georgia 30322.

†Assistant Chief, Anesthesia and Operative Service, Brooke Army Medical Center, San Antonio, Texas.

‡Resident in Anesthesia, Brooke Army Medical Center, San Antonio, Texas.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Paper received: 5/13/75
Accepted for publication: 9/8/75

As there have been no comparative studies of the cardiovascular effects of enflurane and halothane in man, the purpose of the present study was to use systolic time intervals to compare these anesthetic agents, in normal man, in a totally noninvasive manner.

METHODS AND MATERIALS

Two groups, each comprising 6 healthy young patients (all ASA class I), and equally divided between men and women, were studied in a quiet room prior to elective minor surgery. Their mean age was 28 years (range 19 to 39). All had given informed consent and were studied at 0700 hours after an overnight fast. Dextrose in lactated Ringer's solution (1000 ml) was administered IV ½ hour before the study. No premedication was given and no patient was taking any medications.

Awake control measurements of systolic time intervals, blood pressure, and heart rate were recorded. Patients were then preoxygenated for 5 minutes. At that time, 100% N_2O was administered for 60 seconds for a rapid anesthesia induction in order to avoid an excitement stage, and patients were maintained on 50% N_2O-O_2 with either 1% inspired halothane or 2% inspired enflurane by mask. A semiclosed-circle absorber system was used with total gas flow rates of 10 L/min for 5 minutes and then 5 L/min. Spontaneous respirations were maintained throughout the study.

After 30 minutes of stable anesthesia, the following measurements were made: (1) systolic time intervals, (2) blood pressure and heart rate, (3) end-tidal CO_2, and either end-tidal enflurane or halothane (end-tidal gas samples were taken via a 16-gauge catheter placed at the distal tip of a long oral airway), and (4) arterial blood gases. Then the N_2O was discontinued and all measurements were repeated 20 minutes later.

The systolic time intervals were measured by the following standard technic (fig 1): A simultaneous fast-speed recording at 100 mm/sec of a phonocardiogram, carotid arterial pulse wave, and ECG were made on an Electronics for Medicine (EM) monitor. The phonocardiogram was recorded with an EM PS-2 heart-sound microphone placed over the upper precordium to give the best recording of the 2nd heart sound. The carotid arterial pulse wave was recorded with a Statham P23Db pressure transducer attached to a funnel-shaped receiver. The ECG lead with the clearest onset to the QRS complex was chosen.

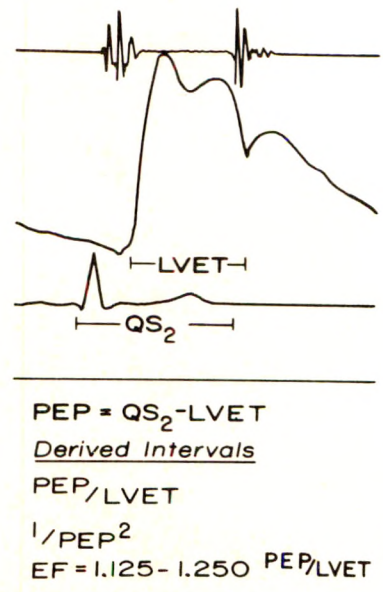


FIG 1. Systolic time intervals measured by the phonocardiogram, carotid arterial pulse trace, and the ECG. Upper part of figure shows how QS_2 and LVET are measured; lower part shows derived parameters.

Three time intervals were measured: (1) total electromechanical systole (QS_2), measured from the Q-wave of the ECG to the first major deflection of the 2nd heart sound; (2) left ventricular ejection time (LVET), measured from the initiation of the carotid upstroke to the dicrotic notch; (3) PEP, calculated by subtracting the LVET from the QS_2. From these measurements, PEP/LVET, $1/PEP^2$, and the ejection fraction were derived. The formula for ejection fraction ($EF = 1.125 - 1.250$ PEP/LVET) was shown by Garrard and associates[8] to have a close correlation ($r = 0.9$) with the ejection fraction measured at cardiac catheterization. All measurements were corrected for heart rate, using Weissler's regression formulas, except for PEP/LVET, which is independent of heart-rate changes between 40 and 110 bpm.[9] All systolic time-interval measurements were made by hand. All values presented are the means of 10 consecutive intervals, which usually included two respiratory cycles.

Statistical comparisons were made using paired *t*-tests within anesthetic groups and unpaired *t*-tests between anesthetic groups.

TABLE 1
Anesthetic and Blood Gas Values of Enflurane and Halothane Groups
(Means ± SE)

Anesthetic agent		End-tidal concentration	Pao_2	$Paco_2$	pH	Base excess
Enflurane	2%	1.23	203.3	48.3	7.32	−2.5
with N_2O	50%	±0.12	±16.0	±2.3	±0.02	±1.4
Enflurane	2%	1.20	425.0	46.3	7.33	−3.0
in O_2		±0.15	±46.3	±2.3	±0.02	±1.5
Halothane	1%	0.65	182.3	40.8	7.36	−2.3
with N_2O	50%	±0.06	±28.0	±2.6	±0.02	±0.6
Halothane	1%	0.70	366.2	40.5	7.34	−3.2
in O_2		±0.06	±54.3	±2.8	±0.01	±0.8

TABLE 2
Basic Cardiovascular Measurements of Enflurane and Halothane Groups
(Means ± SE)

Anesthetic agent		Blood pressure			Heart rate	Cardiac rhythm
		Systolic	Diastolic	Mean		
Enflurane control		127.7	78.0	94.6	69.2	NSR*
		±4.3	±2.1	±1.9	±4.8	
Enflurane	2%	99.7†	61.8†	74.4†	67.0	NSR
with N_2O	50%	±6.5	±2.2	±3.0	±4.6	
Enflurane	2%	105.3†	67.0†	79.8†	73.8	NSR
in O_2		±8.8	±5.1	±6.1	±3.8	
Halothane control		118.4	73.3	89.6	72.2	NSR
		±5.7	±4.2	±3.3	±6.5	
Halothane	1%	107.3‡	66.3‡	80.0‡	65.7	NSR
with N_2O	50%	±5.8	±4.0	±4.2	±4.3	
Halothane	1%	105.7‡	68.7‡	81.0‡	67.8	NSR
in O_2		±6.6	±3.9	±4.7	±3.8	

*NSR = normal sinus rhythm on ECG.
†$p<0.01$ compared with control.
‡$p<0.05$ compared with control.

RESULTS

When given for 45 minutes, both enflurane and halothane resulted in end-tidal concentrations of 0.8 MAC (table 1). The arterial blood gases shown in table 1 indicate a Pao_2 greater than 150 torr at all times during the study. The $Paco_2$ was higher in the enflurane group, but this difference was not statistically significant, due to large patient variability.

Both agents showed a significant decrease in systolic, diastolic, and mean arterial blood pressure (MAP) from their control values (table 2). However, the MAP decreased more in the enflurane group (22%) than in the halothane group (9%). Heart rate did not change significantly in either group. No arrhythmias were seen with either agent.

Of the 3 time intervals measured, PEP is the best indicator of overall myocardial performance. A decrease in myocardial contractility causes a prolongation of PEP and a shortening of LVET. Both agents (fig 2) caused a significant prolongation of PEP ($p<0.05$); however, halothane prolonged PEP significantly more than enflurane

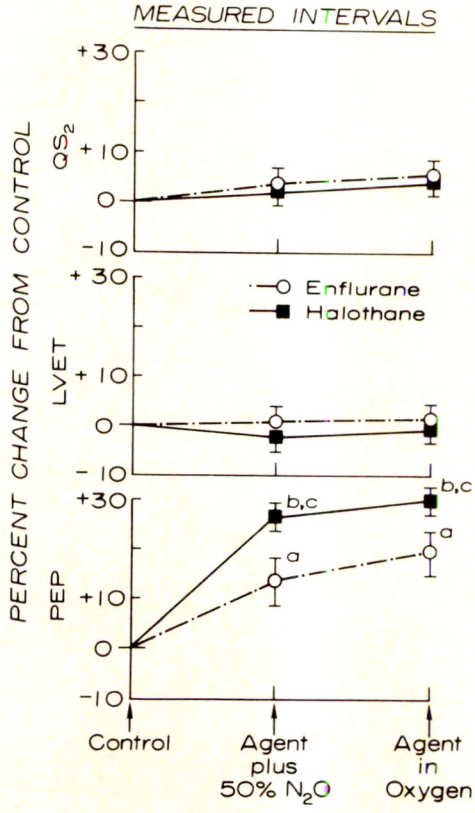


FIG 2. The three measured systolic time intervals shown as percent change from control values. All points represent mean values ± 1 SE of 6 subjects. a = $p < 0.05$ compared with control; b = $p < 0.01$ compared with control; c = $p < 0.05$ compared with enflurane.

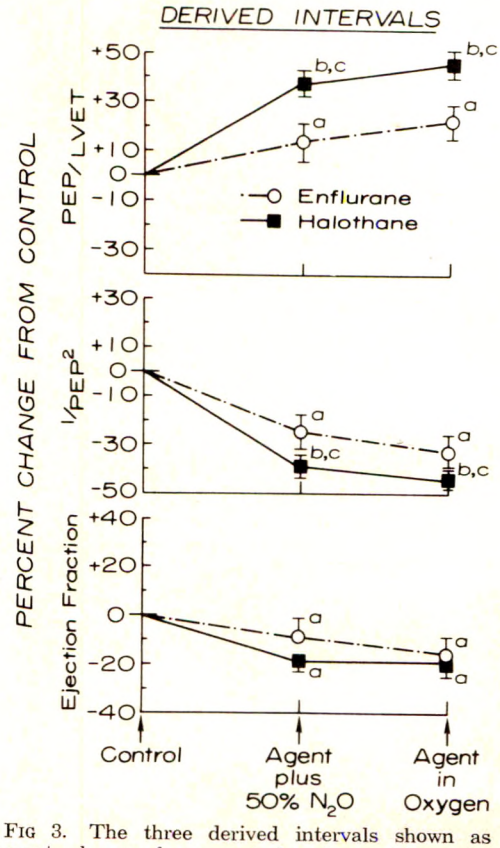


FIG 3. The three derived intervals shown as percent change from control values. All points represent mean values ± 1 SE of 6 subjects. a = $p < 0.05$ compared with control; b = $p < 0.01$ compared with control; c = $p < 0.05$ compared with enflurane.

($p<0.05$). Also, halothane shortened LVET slightly more than enflurane.

In previous studies, measured intervals by themselves have not correlated as well with invasive measurement as have some derived parameters.[7] Thus, figure 3 shows the percent change from control of the three derived intervals. The control values were all within normal limits. Both anesthetic agents caused a significant increase in the PEP/LVET ratio and a significant decrease in $1/PEP^2$ and derived ejection fraction, indicating myocardial depression at equipotent light levels of anesthesia. The difference in PEP/LVET and $1/PEP^2$ between enflurane and halothane was statistically significant ($p<0.05$), with halothane appearing to be the more depressant. PEP/LVET was increased 39.3% by halothane and 14.7% by enflurane, while $1/PEP^2$ was decreased 37.6% by halothane and 22.7% by enflurane.

When N_2O was discontinued, both agents increased PEP and PEP/LVET and decreased $1/PEP^2$ and the ejection fraction. However, these changes were not statistically significant.

DISCUSSION

There have been a number of studies of the cardiovascular effects of halothane in man. Bahlman and associates[3] and Eger and coworkers[10] have shown that 1% end-tidal halothane decreases cardiac output, MAP, and total peripheral resistance (TPR) by 10 to 20%. These investigators, who used the ballistocardiogram to measure myocardial contractility, showed that the IJ wave of the ballistocardiogram was decreased by 25 to 30% with halothane. These changes were all greater with controlled than with spontaneous respirations. The depression they found at light levels of anesthesia (1%) proceeded to profound depression at

deep levels of anesthesia (2%), with the cardiac output, MAP, and IJ wave being depressed 50%.

Morrow[11] measured the effect of halothane on myocardial contractile force by suturing a Walton-Brodie strain gauge to the ventricle during cardiopulmonary bypass. Halothane (2%) administered through the oxygenator for 10 minutes decreased contractile force by 30% and MAP by 15%. Our data are consistent with the above studies, in that halothane decreased contractility, as measured by systolic time intervals, by 30 to 50% and MAP by 11%.

In contrast to halothane, there have been few studies on the cardiovascular effects of enflurane in man. These studies have shown a decreased cardiac output and MAP, with variable TPR results.[1,12] There are no previously recorded measurements of myocardial performance with enflurane in man. Our data show that at equipotent light levels of anesthesia, enflurane decreased contractility as measured by systolic time intervals consistently less than halothane. Halothane increased the PEP/LVET ratio 25% more than did enflurane.

When N_2O was discontinued in both groups, the patients appeared more lightly anesthetized. In spite of this fact, systolic time intervals showed more myocardial depression. This supports previous evidence that at light levels of halothane anesthesia, N_2O acts as a cardiovascular stimulant, probably through activation of the sympathetic nervous system.[13]

Blackburn's group[14] showed that the $Paco_2$ correlates quite well with changes in $1/PEP^2$. In their 5 patients anesthetized with N_2O and curare, a difference in the $Paco_2$ of 6 torr, as we found between the halothane and enflurane groups, produced a 15% difference in $1/PEP^2$. The $Paco_2$ difference between our 2 groups just failed to be statistically significant at the $p<0.05$ level; however, it may have been physiologically quite significant. At a lower $Paco_2$ of 40 torr, enflurane may appear to be more depressant than it did in this study.

The isovolumic contraction time used in the past to measure myocardial performance is related to the 1st heart sound, which has been shown to occur at a variable time from the onset of left ventricular contraction.[15] Recently, attention has focused on the preejection period as the interval to be measured to assess intrinsic myocardial performance. There are 4 determinants of the duration of the preejection period: (a) left ventricular contractility; (b) left ventricular end-diastolic pressure (preload); (c) aortic diastolic pressure (afterload); and (d) heart rate.

The effect of changes in heart rate on PEP was eliminated in our study by using regression formulas relating systolic time intervals to heart rate, derived by Weissler from multiple observations of both normal individuals and cardiac patients.[9]

Talley and coworkers[16] showed that PEP is only slightly affected by changes in aortic diastolic pressure, and that a change of 39 torr in the aortic diastolic pressure caused only a 7 msec (6%) change in PEP. In our study, the diastolic blood pressure decreased only 7 torr with halothane and 17 torr with enflurane and therefore should have had minimal effects on PEP.

Reitan and associates[17] reported that $1/PEP^2$ correlated well with peak ascending aortic blood flow acceleration, a good measurement of myocardial contractility, Noble and coworkers[18] having previously observed that changes in ventricular preload and afterload caused little variation in peak blood flow acceleration. Drawing from these conclusions, we feel that PEP, PEP/LVET, and $1/PEP^2$ were minimally affected by the difference in afterload in the halothane and enflurane groups.

Accepting that PEP was only minimally affected by changes in heart rate and afterload, the changes we have observed in PEP/LVET and the ejection fraction during anesthesia could reflect changes either in preload or in the inotropic state of the heart. Talley[16] showed that PEP is markedly affected by changes in ventricular end-diastolic pressure. Our study cannot separate these two factors, since measurements of the pulmonary capillary wedge pressure, left atrial pressure, or left ventricular end-diastolic pressure (LVEDP) would be needed to do this. However, if enflurane is not less depressant than halothane, our findings mean that enflurane must have raised the LVEDP more than did halothane. We do not believe this happened, since enflurane appears to produce more peripheral vasodilation and would be expected, therefore, to lower LVEDP.

Our findings probably indicate a difference in the inotropic state of the heart with

the 2 anesthetic agents. Therefore, while the lower MAP seen with enflurane is due in part to some decrease in contractility, it appears mainly due to a decrease in TPR, while the decrease seen with halothane is primarily caused by a decrease in contractility and thus by decreased cardiac output.

REFERENCES

1. Marshall BE, Cohen PJ, Klingenmaier CH, et al: Some pulmonary and cardiovascular effects of enflurane anaesthesia with varying $Paco_2$ in man. Br J Anaesth 43:996-1002, 1971

2. Prys-Roberts C, Kelman GR, Greenbaum R, et al: Hemodynamics and alveolar-arterial Po_2 differences at varying $Paco_2$ in anesthetized man. J Appl Physiol 25:80-87, 1968

3. Bahlman SH, Eger EI II, Halsey MJ, et al: The cardiovascular effects of halothane in man during spontaneous ventilation. Anesthesiology 35:494-502, 1972

4. Shimosato S, Sugai N, Iwatsuki N, et al: The effect of Ethrane on cardiac muscle mechanics. Anesthesiology 30:513-518, 1969

5. Kemmotsu O, Hashimoto Y, Shimosato S: The effects of fluroxene and enflurane on contractile performance of isolated papillary muscles from failing hearts. Anesthesiology 40:252-260, 1974

6. Brown RB, Crout JR: A comparative study of the effects of five general anesthetics on myocardial contractility. Anesthesiology 34:236-245, 1971

7. Martin CE, Shaver JA, Thompson ME, et al: Direct correlation of external systolic time intervals with internal indices of left ventricular function in man. Circulation 44:419-431, 1971

8. Garrard CL, Weissler AM, Dodge HT: Relationship of alteration in systolic time intervals to ejection fraction in patients with heart disease. Circulation 42:455-462, 1970

9. Weissler AM, Harris WS, Schoenfeld CD: Systolic time intervals in heart failure in man. Circulation 37:149-159, 1968

10. Eger EI II, Smith NT, Stoelting RK, et al: Cardiovascular effects of halothane in man. Anesthesiology 32:396-409, 1970

11. Morrow DH, Morrow AG: The effects of halothane on myocardial contractile force and vascular resistance. Anesthesiology 22:537-541, 1961

12. Graves CL, Downs NH: Cardiovascular and renal effects of enflurane in surgical patients. Anesth & Analg 53:898-903, 1974

13. Smith NT, Eger EI II, Stoelting RK, et al: The cardiovascular and sympathomimetic responses to the addition of nitrous oxide to halothane in man. Anesthesiology 32:410-421, 1970

14. Blackburn JP, Conway CM, Leigh JM, et al: $Paco_2$ and the pre-ejection period. Anesthesiology 37:268-276, 1972

15. Dibartolo G, Nunez-Day D, Muiesan G, et al: Hemodynamic correlation of the first heart sound. Am J Physiol 201:888-892, 1961

16. Talley RC, Meyer JF, McNay JL: Evaluation of the pre-ejection period as an estimate of myocardial contractility in dogs. Am J Cardiol 27:384-391, 1971

17. Reitan JA, Smith NT, Borison VS, et al: The cardiac pre-ejection period. Anesthesiology 36:76-80, 1972

18. Noble MI, Trenchard D, Guz A: Left ventricular ejection in conscious dogs: I. Measurement and significance of the maximum acceleration of blood from the left ventricle. Circ Res 19:138-147, 1966

NEFOPAM Nefopam is an analgesic unrelated chemically and structurally to any other analgesic. Its analgesic potency is about half that of morphine. The ventilatory response to CO_2 was studied in 6 volunteers. The mean displacement to the right following 5 and 10 mg morphine was 2.98 and 3.76 torr PCO_2, respectively, while following 20 and 40 mg nefopam was 1.44 and 1.90 torr PCO_2 respectively. The difference between the drugs was statistically significant. A high incidence of nausea after nefopam may have resulted in a tendency for subjects to overventilate. *(Gasser JC, Bellville JW: Respiratory effects of nefopam. Clin Pharm Ther 18:175-179, 1975)*

Effect of P_{aCO_2} on O_2 Consumption During Cardiopulmonary Bypass in Man

RICHARD W. PATTERSON, MD*

Under conditions of anesthesia with controlled respiration, the changes in the state of the circulation due to altered P_{aCO_2} are often overlooked or attributed to the anesthetic agent. During cardiopulmonary bypass when cardiac output is kept constant, change in fluid level of the extracorporeal reservoir reflects overall change in the circulatory beds.

Following an hour on total bypass for stabilization of all parameters, a change in the oxygenator ventilating-gas mixture was induced to increase or decrease the P_{aCO_2} an average of 11 torr in 40 patients. A reduction in P_{aCO_2} from 37 to 25 torr increased mean arterial blood pressure (MAP), central venous pressure (CVP), and the volume of blood stored in the extracorporeal circuit, signifying an overall reduction in the intravascular capacity. This was associated with a decrease in total O_2 consumption ($\dot{V}O_2$). An abrupt increase of P_{aCO_2} from 26 to 37 torr produced a decrease in MAP, in CVP, and in the reservoir blood level, signifying blood "take up" by the patient. There was also an associated increase in $\dot{V}O_2$.

CARBON DIOXIDE tension affects both the blood supply[1-3] and metabolic rate,[4,5] two major determinants of the O_2 consumption ($\dot{V}O_2$) of a tissue, organ, or of the whole body. The two effects may not be concordant. For example, an increase in total body $\dot{V}O_2$ can be produced by respiratory alkalosis,[6,7] a situation which in itself selectively decreases the blood flow in several circulatory beds.[8,9]

This study, conducted during cardiopulmonary bypass in man, describes the changes in whole body $\dot{V}O_2$ and the whole body blood volume shifts that occur following a modest (11 torr) change from one CO_2 steady state to another.

METHODS AND MATERIALS

Forty patients (14 women, 26 men) in AHA classes II and III, undergoing surgical correction of acquired heart disease with the aid of total cardiopulmonary bypass, were studied. Ages ranged from 40 to 61 years and body surface area (BSA) from 1.7 to 2.2 sq m. Premedication consisted of 100 mg of secobarbital and 0.5 mg of scopolamine, given IM 60 minutes before induction. Anesthesia was induced with 200 to 450 mg of thiopental IV, and a cuffed endotracheal tube was placed after IV administration of 100 mg of succinylcholine. Anesthesia was maintained with 1% halothane in O_2.

The heart was approached through a midline sternotomy and the pericardium was opened. Venous catheters were inserted into the venae cavae through a right atriotomy. The arterial line from the extracorporeal oxygenator to the patient was inserted into the ascending aorta. A roller pump-bubble oxygenator (Bentley) provided a pump output ($\dot{Q}p$) of approximately 2.3 L/min/sq m BSA. The pump was initially primed with 1000 ml of ACD whole blood (heparin, calcium gluconate, and tris buffer added), 500 ml of lactated Ringer's, and 500 ml of 5% D/W. During the bypass interval, 1% halothane was continuously administered via a

*Professor of Anesthesiology, Department of Anesthesiology, The Center for the Health Sciences, UCLA School of Medicine, University of California, Los Angeles, California 90024.

This study was supported in part by NIH Grant HL 17358-01.

Paper received: 11/27/74

Accepted for publication: 8/26/75

Fluotec® vaporizer inserted in the extracorporeal oxygenating circuit. The total gas flow through this circuit varied from 10 to 14 L/min between patients but was held constant for each individual patient. Through change of water temperature in the heat exchanger, all patients were internally cooled or warmed, as measured by an esophageal thermistor placed in the midesophagus.

The ventilating gas was either 100% O_2 or a mixture of O_2-CO_2 (98:2). Switch from one to the other did not alter the total gas flow rate.

In one group of patients, bypass was initiated using the O_2-CO_2 ventilating mixture, which was continued for the entire 1st hour, during which perfusion stabilized to constant output, constant arterial and venous pressures, and constant equilibrium volume between the patient and the extracorporeal circuit. Temperature also stabilized during this time. $\dot{Q}p$ was not changed during the study period. Arterial and mixed venous blood samples were drawn from the pump-oxygenator lines, iced, and rapidly analyzed for $Paco_2$, pH, and Pao_2 by a Model 113 Instrumentation Laboratories blood-gas analyzer, with corrections made for temperature differences between patient and analyzer. From these measured values, O_2 content was derived and used in conjunction with the constant $\dot{Q}p$ to calculate O_2 consumption by the Fick equation. Subsequently, $Paco_2$ was abruptly reduced by switching the extracorporeal circuit ventilating gas to 100% O_2. Blood samples were drawn at the end of 30 minutes and analyzed as before.

In another group of patients, bypass was initiated using 100% O_2 as the ventilating mixture for the 1st hour, then switching to the O_2-CO_2 mixture.

The statistical significance of the changes in mean arterial blood pressure (MAP), mean central venous pressure (MCVP), change in bypass reservoir volume, and $\dot{V}o_2$ was determined by Student's *t*-test for paired data. The values obtained after 1 hour of constant esophageal temperature on bypass were compared with those obtained 30 minutes after the induced change in $Paco_2$.

During 6 operations in which the body temperature was maintained at a constant value for 2 hours or more, the ventilating gases were repeatedly alternated at 30-minute intervals.

RESULTS

During the bypass observation period, average body temperature of all patients was 34 (range 32 to 37 C), and the average hematocrit was 34% (range 28 to 36).

After a steady state had been established, change in $Paco_2$ resulted within several minutes in changes in MAP, MCVP, and redistribution of blood between the extracorporeal reservoir and the patient. These vascular changes persisted during the 30-minute interval until the venous and arterial blood samples were drawn.

Switching the extracorporeal gas mixture from CO_2-O_2 to 100% O_2 (table 1) produced an average $Paco_2$ decrease of 12 torr from an average baseline of 37 torr. With $\dot{Q}p$ remaining constant, MAP increased (average 23 torr), MCVP increased (average 3 torr), the volume of blood stored in the extracorporeal reservoir increased (average of 400 ml), and the total body $\dot{V}o_2$ decreased an average of 7 ml/min/sq m.

Starting from an average $Paco_2$ of 26 torr, changing the ventilating gas from a mixture containing only O_2 to one containing CO_2-O_2 (table 2) increased the average $Paco_2$ by 11 torr and resulted in a decrease in MAP, MCVP, and extracorporeal reservoir blood level (400 ml), and increased average total body $\dot{V}o_2$ 8 ml/min/sq m.

An example of values obtained in a 40-year-old man (figure) shows the repeatable changes in venous and arterial pressures, reservoir volume, and $\dot{V}o_2$ that resulted as the $Paco_2$ was altered from high CO_2 (2) to low (0) to high (2) and again to low (0) at half-hour intervals over a 2-hour period during which $\dot{Q}p$ was constant. Similar responses to changes in $Paco_2$ were observed in the other 5 patients studied for as long as 2 hours.

DISCUSSION

Study during cardiopulmonary bypass eliminated direct CO_2-cardiac effects[10] and tested the effect of CO_2 changes on the peripheral circulation and/or related alterations of body metabolism. Keeping the $\dot{Q}p$ constant throughout the observation period accentuated the overall vascular changes by eliminating the usual response of the pump running on automatic control to changes in reservoir volume or the response of the perfusionist to vascular-pressure changes. In a situation where CO_2 is being eliminated, the MABP abruptly increasing concurrently

TABLE 1

Vascular Changes After a Step Decrease in $Paco_2$ During Cardiopulmonary Bypass

	Temperature, C	$Paco_2$, torr		Vo_2, ml/min/sq m		BP, torr		CVP, cm H_2O		Reservoir volume (X100), ml	
		A*	B†	A	B	A	B	A	B	A	B
1	34	34	23	90	79	60	90	5	12	14	19
2	34	34	26	121	100	70	80	5	10	10	17
3	32	35	25	66	68	70	75	4	4	13	15
4	32	34	23	75	76	60	65	5	5	10	11
5	37	36	26	81	75	60	100	4	9	11	17
6	37	34	26	86	75	60	90	5	10	12	19
7	36	33	26	75	74	80	80	4	4	10	11
8	36	37	22	80	70	60	100	4	8	9	14
9	34	37	22	62	55	75	100	4	10	10	16
10	32	34	28	56	53	70	70	5	6	11	12
11	32	42	25	65	57	60	90	5	7	10	14
12	32	31	20	89	75	70	100	6	10	10	16
13	34	42	25	95	90	60	85	5	5	11	13
14	34	35	28	90	86	60	90	6	10	11	14
15	37	37	27	100	92	70	100	4	10	10	19
16	32	43	26	83	85	60	70	3	6	11	15
17	34	36	26	58	62	60	80	7	9	11	13
18	34	36	26	104	96	60	100	6	8	10	15
19	34	38	25	108	106	80	80	6	10	13	15
20	37	40	24	92	82	60	90	4	8	10	15
21	32	38	24	88	76	60	100	5	5	9	13
22	32	40	28	96	88	60	95	4	9	11	15
23	34	36	25	90	78	70	95	5	10	11	17
Mean	34	37	25	85	78	65	88	5	8	11	15
SE		0.6	0.4	3.4	2.8	1.4	2.3	0.2	0.5	0.25	0.48
p		<0.001		<0.001		<0.001		<0.001		<0.001	

*A, values obtained after 1 hour of constant esophageal temperature on bypass.

†B, values obtained 30 minutes after induced change in $Paco_2$.

with an increase in CVP would ordinarily prompt the perfusionist to reduce the pump flow rate, consequently restoring the pressures to original values. Switching from O_2 to CO_2, MAP decreases and the volume decreases in the reservoir, and the usual maneuver is to add volume to the system and increase $\dot{Q}p$, thus increasing the pressure. No case is included in this study that required a change in pump rate or the addition of volume expanders to compensate for changes in volume shifts or arterial pressure.

The changes described resulted from a relatively small $Paco_2$ alteration within the total range of 20 to 40 torr, the usual operating area during cardiopulmonary bypass, and demonstrate an additional determinant of the distribution of blood flow[11] and of

TABLE 2

Vascular Changes After a Step Increase in $Paco_2$ During Cardiopulmonary Bypass

	Temperature, C	$Paco_2$, torr		Vo_2, ml/min/sq m		BP, torr		CVP, cm H_2O		Reservoir volume (X100), ml	
		A*	B†	A	B	A	B	A	B	A	B
1	34	30	41	96	103	90	70	11	6	25	21
2	32	30	40	55	58	70	70	5	5	23	23
3	34	30	36	90	98	80	65	8	4	22	19
4	34	27	37	82	90	80	70	9	6	25	22
5	37	26	36	89	86	80	80	4	6	20	22
6	34	24	35	83	92	90	75	10	5	22	16
7	34	30	41	58	62	80	75	8	6	19	16
8	37	33	41	96	104	80	70	11	7	30	25
9	37	20	36	119	137	100	50	12	6	20	16
10	32	25	32	75	91	90	50	12	7	20	15
11	34	25	34	100	110	90	65	10	5	25	20
12	34	28	40	85	94	90	55	10	4	20	16
13	34	26	38	82	93	85	40	8	6	22	18
14	34	26	36	79	96	90	40	9	6	23	17
15	36	26	39	88	92	90	50	11	5	30	24
16	36	25	36	78	84	100	60	11	4	20	16
17	34	25	37	76	85	100	50	10	6	19	15
Mean	34	26	37	84	92	87	60	9	5	22	18
SE		0.7	0.6	3.6	4.2	2	3	0.5	0.2	0.83	0.81
p		<0.001	<0.001	<0.001		<0.001		<0.001		<0.001	

*A, values obtained after 1 hour of constant esophageal temperature on bypass.

†B, values obtained 30 minutes after induced change in $Paco_2$.

$\dot{V}o_2$ during bypass.[12] When $Paco_2$ was decreased and vascular redistribution occurred, blood was stored extracorporeally, an option denied the intact body, which may account in part for the failure to demonstrate the increases in $\dot{V}o_2$ reported with hypocapnia.[6,7,13]

The vascular changes due to the relative changes in $Paco_2$ are in agreement with previous investigations concerning the role of CO_2 in circulatory dynamics.[1,14,15] When $Paco_2$ was increased from the baseline of the hypocapnic situation, $\dot{V}o_2$ was increased as the patient's blood volume was expanded and perfused at low venous and arterial pressures. Vascular changes were in most instances more pronounced than the quantitative changes in $\dot{V}o_2$, and the greatest change in circulatory volume was not necessarily reflected in a similar change in $\dot{V}o_2$; this is consistent with the findings of Stainsby and Otis[16] in regard to blood flow and O_2 uptake in skeletal muscle.

REFERENCES

1. Kittle CF, Aoki H, Brown EB Jr: The role of pH and CO_2 in the distribution of blood flow. Surgery 57:139-154, 1965

2. Straub PW, Buhlman AA: Reduction of blood volume by voluntary hyperventilation. J Appl Physiol 29:816-817, 1970

3. Feinberg H, Gerola A, Katz LN: Effect of changes in blood CO_2 level on coronary flow and myocardial O_2 consumption. Am J Physiol 199: 349-354, 1960

4. Ranson SL, Walker DA, Clarke ID: Effects

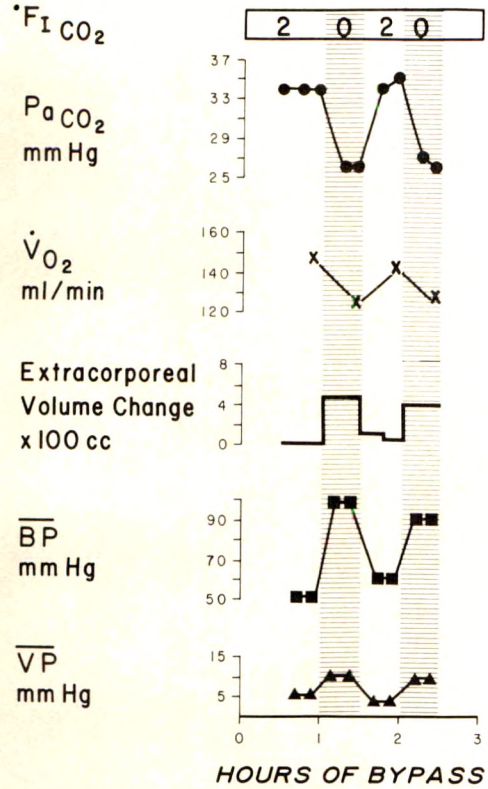


FIGURE. Repeatable changes in vascular volume shift, vascular pressures, and whole body $\dot{V}o_2$ as CO_2 concentration is switched at half-hour intervals from 0 to 2% in bypass oxygenator ventilating-gas mixture in 40-year-old man; CONSTANTS: temperature (35 C), hematocrit, 1% halothane anesthesia, pump output. Extracorporeal volume change refers to changes in oxygenator blood level, using initial hypocapnic state as reference level.

of carbon dioxide on mitochondrial enzymes. Biochem J 76:216-221, 1960

5. Chalazonitis N, Arvanitaki A: Neuromembrane electrogenesis during changes in Po_2, Pco_2, pH, Biochemistry of Simple Neuronal Models. Edited by E Costa, E Giacobini. New York, Raven Press, 1970, vol 2

6. Cain SM: Increased oxygen uptake with passive hyperventilation of dogs. J Appl Physiol 28:4-7, 1970

7. Karetzky MS, Cain SM: Effects of carbon dioxide on oxygen uptake during hyperventilation in normal man. J Appl Physiol 28:8-12, 1970

8. Kety SS, Schmidt CF: The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. J Clin Invest 27:484-492, 1948

9. Vance JP, Brown DM, Smith G: The effects of hypocapnia on myocardial blood flow and metabolism. Br J Anaesth 45:455-463, 1973

10. Carson SAA, Chorley GE, Hamilton FN, et al: Variation in cardiac output with acid-base changes in the anesthetized dog. J Appl Physiol 20:948-953, 1965

11. Less MH, Herr RH, Hill JD, et al: Distribution of systemic blood flow of the rhesus monkey during cardiopulmonary bypass. J Thorac Cardiovasc Surg 61:570-586, 1971

12. Shepard RB, Kirklin JW: Relation of pulsatile flow to oxygen consumption and other variables during cardiopulmonary bypass. J Thorac Cardiovasc Surg 58:694-702, 1969

13. Khambatta HJ, Sullivan SF: Effect of respiratory alkalosis on oxygen consumption and oxygenation. Anesthesiology 38:53-58, 1973

14. Richardson DW, Wasserman AJ, Patterson JL: General and regional circulatory response to change in blood pH and carbon dioxide tension. J Clin Invest 40:31-43, 1961

15. Kontos HA, Richardson DW, Patterson JL: Role of hypercapnia and acidosis in the vasodilator response to hypercapnic acidosis. Am J Physiol 215:1406-1408, 1968

16. Stainsby WN, Otis AB: Blood flow, blood oxygen tension, oxygen uptake, and oxygen transport in skeletal muscle. Am J Physiol 206:858-866, 1964

DOPAMINE VS DOBUTAMINE The cardiac and systemic hemodynamic effects of dopamine and dobutamine were measured in anesthetized dogs. Dopamine increased HR only when infusion rates reached 10 μg/kg/min while dobutamine produced dose related increases between 2 and 32 μg/kg/min. Dopamine increased mean arterial pressure at infusion rates above 5 μg/kg/min while no change occurred with dobutamine at any dose. Dobutamine increased cardiac output more than dopamine. Dopamine infusions up to 10 μg/kg/min increased renal and mesenteric blood flow while dobutamine had negligible effects. These data confirm that both these sympathomimetic amines exert positive inotropic effects but cause different responses in the peripheral vasculature. *(Robie NW, Goldberg LI: Comparative systemic and regional hemodynamic effects of dopamine and dobutamine. Am Heart J 90:340-345, 1975)*

Questions and Answers

We invite you to submit questions to the Editorial Office, Kahler East, Suite C, Rochester, Minnesota 55901. The names of those submitting questions will remain anonymous if so desired.

The answers will be prepared by competent authorities, and their names will or will not appear, according to their specific wishes.

Ronald W. Dunbar, M.D.
Contributing Editor
Atlanta, Georgia

* * *

QUESTION: *Please comment on the use of $NaHCO_3$ with the administration of bank blood. I am familiar with the recommendation of Howland as to the administration of $NaHCO_3$; however, our surgeons recently have said their literature now states this is contraindicated.*

MD, Michigan

ANSWER #1: ". . . anesthetists must be ever alert to the patient as an individual with his own peculiar responses to stress. This means that rigid application of routines for management must be avoided."[1]

"The occurrence or severity of metabolic acidosis in patients requiring massive blood transfusion is not predictable; thus the routine administration of bicarbonate is not warranted."[2]

Administration of bicarbonate should be governed by the patient's acid-base status. Although Howland routinely administers 44.6 mEq of $NaHCO_3$ for every 5 units of bank blood, he states: "If blood gas studies are continuously available, sodium bicarbonate can be given only as required."[3]

If blood-gas studies are not available, the question becomes more complex. Under such circumstance, the decision to administer $NaHCO_3$ should be governed by the patient's circulatory status—that is, a warm, pink, dry patient probably doesn't need $NaHCO_3$ *empirically;* a hypoperfused patient may.[4]

The hazards of routine administration of $NaHCO_3$ during massive blood transfusion include: (1) worsening of posttraumatic alkalosis with well-known effects on the oxyhemoglobin-dissociation curve, increased myocardial irritability, and possibly vasoconstriction,[5] and (2) increased Na load in patients with sodium-retaining tendencies.

I recommend Miller's review on "Transfusion Therapy and Associated Problems," in vol 1 of the ASA Regional Refresher Courses in Anesthesiology, for a brief, concise review of the problem.

REFERENCES

1. Cullen SC, Larson CP Jr: Essentials of Anesthetic Practice. Chicago, Year Book Medical Publishers, Inc, 1974, p 4

2. Miller RD, Tong MS, Robbins TO: Effects of massive transfusion of blood on acid-base balance. JAMA 216:1762-1765, 1971

3. Howland WS, Schweizer O, Gould P: Massive blood replacement. Acute Fluid Replacement in the Therapy of Shock. Edited by TI Malinin, R Zepps, W Drucker, HB Callahan. New York, Stratton Intercontinental Medical Book Corp, 1974, p 105-109

4. Collins JA, Simmons RL, Collins PM, et al: Acid-base status of seriously wounded combat casualties: II. Resuscitation with stored blood. Ann Surg 173:6-18, 1971

5. Lyons JH Jr, Moore FD: Posttraumatic alkalosis: incidence and pathophysiology of alkalosis in surgery. Surgery 60:93-105, 1966

R. Dennis Bastron, MD
Department of Anesthesiology
University Hospital
Iowa City, Iowa

* * *

ANSWER #2: All references to blood transfusion should specify rates. Administration of 10 units of bank blood in 10 hours or in 30 minutes obviously present different situations. Also, if the patient's acid-base status can be assessed after every 5 units of bank blood, no routine administration of $NaHCO_3$ is necessary. We have attempted avoiding buffering during rapid blood replacement, as

suggested by Miller and associates,[1] and found that our patients became acidotic. The dangers of alkalinization of patients are mainly theoretic; using routinely 44.6 mEq of $NaHCO_3$ for every 5 units of bank blood, marked metabolic alkalosis does not occur.

In our last 22 patients given 32.8 ± 13.7 units of CPD blood, the pretransfusion blood level of CO_2, 26.4 ± 2.5 mEq/L, was raised at the end of transfusion (20 to 78 units) to only 31.8 ± 4.1 mEq/L, a figure only slightly elevated beyond the normal range in our laboratory (26 to 29 mEq/L). This moderate alkalosis is certainly preferable in our opinion to the dangers of acidosis. It should also be noted that there is a marked difference in the basic cardiovascular status of young servicemen and middle-aged and elderly cancer patients.[2]

REFERENCES

1. Miller RD, Tong MJ, Robbins TO: Effects of massive transfusion or whole blood on acid-base balance. JAMA 216:1762-1765, 1971

2. Howland WS, Schweizer O, Boyan CP: The effect of buffering on mortality of massive blood replacement. Surg Gynecol Obstet 121:777-782, 1965

William S. Howland, MD
Department of Anesthesiology
Memorial Center for Cancer and Allied Diseases
New York, New York

* * *

QUESTION: *Kindly advise me on the usefulness of preoperative determination of blood volume.*

MD, Massachusetts

ANSWER #1: Blood-volume measurements, forgotten in many hospitals, are extremely useful in the management of selected patients undergoing surgical procedures. At Memorial Hospital we recommend that initial baseline measurements be done in those patients in whom:

1. Unusual blood or fluid loss can be expected during surgical intervention.
2. Cardiac insufficiency or metabolic disturbances result in body fluid imbalance.

If circulatory instability then ensues during the hospital stay, subsequent determinations are an aid in patient management.

Blood-volume measurements are not universally accepted, however, as essential in patient care. There are several reasons for this:

1. Many clinicians feel that if they are able to measure central venous pressure (CVP) and monitor urine output, they are able to control most acute situations. It is entirely possible, however, for a heart to fail in association with a contracted blood volume. The rising CVP and decreasing urine output may then be misinterpreted.

2. A common criticism is that blood-volume measurements are inaccurate, especially those done with plasma tags. We found that they are highly reproducible if scrupulous attention is paid to technic.

3. Tracer loss with blood or plasma can be a problem during acute situations. This problem, too, can be lessened to some extent if samples are drawn at 10, 15, and 20 minutes and results extrapolated to zero time.

4. Isolated blood-volume measurements are of questionable help in that obesity, weight loss or gain, extremes of age, and sex alter so-called normal values. For that reason, we feel it is essential to do serial determinations, starting with a baseline if possible, in our complicated fluid-balance problems.

Although the usual surgical patient can be managed by monitoring vital signs, urine output, and CVP, blood-volume measurements are important in caring for patients with extraordinary fluid and circulatory problems.

Patricia Underwood, MD
William S. Howland, MD
Department of Anesthesiology
Memorial Center for Cancer and Allied Diseases
New York, New York

* * *

ANSWER #2: One major advantage of preoperative blood-volume measurement is definition not only of total circulating blood volume but also quantification of the plasma and red-cell fractions, giving more information than just hemoglobin and hematocrit determinations. For example, low hemoglobin and hematocrit values can be associated with a high blood volume composed of a normal red-cell volume and a high plasma volume. Thus the apparent anemia indicated by a low hemoglobin value is misleading. Second, by knowing the actual preoperative

plasma and red-cell volumes, the adequacy of transfusion can be checked postoperatively against an accurate standard for each individual patient. This allows additional transfusion therapy with the most appropriate blood component, reducing the risk to the patient of overtransfusion and exposure to blood-group antigens. Just as important, it allows more efficient use of blood-bank resources.

Sheila M. Muldoon, MD
Department of Anesthesiology
Mayo Clinic
Rochester, Minnesota

* * *

QUESTION: *A 65-year-old hypertensive patient is on diuretic therapy and in generally good health. Potassium is 3 mEq/L (normal = 3.5 to 5 mEq/L). He is having an elective herniorrhaphy. Please indicate management if: (a) Patient is seen in the operating room just before proposed operation (when K^+ results have just come back); (b) On preoperative rounds the night before operation; (c) Several days prior to proposed operation. Would a K^+ of 2.5 mEq/L alter your management? How would you manage a patient with low K^+ for emergency surgery? Should all patients on diuretic therapy have preoperative electrolytes determined?*

MD, Georgia

ANSWER #1: Chronic diuretic therapy with K^+ depletion presents a serious hazard to the patient on digitalis therapy and occasionally when the need arises to reverse the action of muscle relaxants. A rigid approach to this predicament is impossible; we can only propose certain useful guidelines. Serum electrolyte concentrations are at best a poor guide to the magnitude of K^+ depletion.

Total body potassium content in the human adult is approximately 4000 mEq, of which 1% is in the extracellular compartment.[1] Enormous deficits may accrue with a relatively small decrease in serum K^+, which emphasizes the difficulty encountered in the evaluation of potassium balance. Although some anesthesiologists may succumb to the temptation and cancel the planned operation in circumstances described under (a), such a unilateral move is not necessarily warranted or useful. First, a decision as to replacement therapy must be formulated clearly if the patient is to be anesthetized at a future date. Clearly, an objective evaluation of K^+ repletion requires close measurement of potassium intake and output, a project not recommended for routine use. Given the conditions described, a patient in good health who requires an elective herniorrhaphy and whose serum K^+ is 3 mEq/L can be operated on under regional or general anesthesia. If there is concern regarding fluctuations in the serum K^+, samples may be drawn during and immediately following operation. Potassium is a potentially lethal drug. In a non-digitalized patient and in the absence of cardiac arrhythmias I prefer not to start replacement therapy while the serum K^+ has decreased to 2.5 mEq/L.

Unfortunately, even under ideal conditions, most laboratories will not report results back in less than 60 minutes, thereby making acute replacement difficult. If desired, additional K^+ can be administered IV as KCl solution at a rate not to exceed 0.2 mEq/kg/hr through a central venous line. (Potassium solutions must never be administered through a peripheral IV).

If the patient is seen several days before operation, an increase in oral K^+ replacement is advisable. Such therapy is best not carried out for more than 2 to 3 days, as it has been known to result in intestinal ulceration.

If the serum K^+ is below 2.5 mEq/L or emergency surgery is required, an IV infusion is in order, as indicated above, followed by repeated measurements of serum K^+ at 2-hour intervals until the concentration has stabilized in the normal range. Although objective reasons can be listed why any one mode of anesthesia is to be preferred over another, the choice is generally subjective, and good data on morbidity are unavailable.

Digitalis toxicity and emergency surgery are not an infrequent combination. In this setting, anesthetics should be chosen carefully, in view of the propensity to lethal cardiac arrhythmias during transient episodes of hypokalemia. Except for the patient with massive burns, extensive muscle wasting secondary to neurologic disease, chronic renal failure, or acute metabolic acidosis following circulatory arrest intraoperatively, hypokalemia is more common than appreciated.

Intraoperative monitoring of serum K^+ is not yet considered a routine procedure in the critically ill except for open-heart surgery. Until such time that these measurements will be available, it is likely that disturbances of cardiac rhythmicity during

emergency operations may not be recognized as being secondary to hypokalemia.

Myron B. Laver, MD
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts 02114

REFERENCE

1. Maxwell MH, Kleeman CL: Clinical Disorders of Fluid and Electrolyte Metabolism. Second edition. New York, McGraw-Hill Book Company, 1972

* * *

ANSWER #2: The case presents a difficult clinical question. While it would be generally agreed that severe hypokalemia increases the incidence of cardiac arrhythmias, the risk of moderate levels of hypokalemia combined with the pharmacologic and physiologic trespass of anesthesia and surgery is not well established. Levels of serum K^+ not hazardous in the unanesthetized patient may cause serious problems during anesthesia. Acute changes in serum K^+ occur in response to commonly used anesthetic agents and neuromuscular-blocking drugs.[1,2]

Respiratory alkalosis and acidosis during anesthesia can effect serum K^+ and may initiate cardiac arrhythmias.[3] Low extracellular K^+ and the resultant increased rate of diastolic depolarization[4] may potentiate, or increase in frequency, ventricular arrhythmias, which occur commonly during anesthesia. Whether the hazard of arrhythmia is due to the low serum K^+, total body potassium depletion, or to an abnormal ratio of intracellular:extracellular K^+ is not clear.

However, even a small risk of increase in potentially hazardous cardiac arrhythmias indicates delay in elective surgery to permit replacement therapy, allowing adequate time for equilibration, particularly in patients who have a history compatible with total body potassium depletion.

Therefore, in this patient with vascular disease and on chronic diuretic therapy, it would be wise to postpone elective surgery to allow for replacement therapy even though hypokalemia is recognized shortly before scheduled operation. We prefer to use an oral replacement with a liquid preparation of KCl, with which it is usually possible to correct moderate hypokalemia in 24 to 48 hours. A repeat serum K^+ and an ECG rhythm strip should be obtained to ascertain adequacy of treatment prior to proceeding with the operation.

Although it is not possible to adequately set limits of serum K^+ for elective surgery, we have used 3.2 mEq/L as an accepted level in otherwise healthy patients without ECG evidence of hypokalemia. However, clinical judgment must prevail in these borderline cases, since definitive safe levels have not been established.

In a patient scheduled for emergency surgery, K^+ depletion should be corrected prior to operation, when possible, as should other electrolyte and acid-base abnormalities, always weighing the risk of delay against the urgency of the surgical procedure. ECG monitoring should accompany attempts to rapidly replace K^+ by the IV route.

Since most diuretic therapy leads to increased K^+ excretion and potentially to K^+ depletion, patients on diuretic therapy should have preoperative electrolyte determination.

Carl A. Smith, MD
Director
Department of Anesthesiology
Crawford W. Long Memorial Hospital
Atlanta, Georgia

REFERENCES

1. Famby NR, Gissen AJ, Savarese JJ, et al: Decamethonium and serum potassium in man. Anesthesiology 42:692-697, 1975

2. Wong KC, Wetstone D, Martin WE, et al: Hypokalemia during anesthesia: the effects of d-tubocurarine, gallamine, succinylcholine, thiopental, and halothane with or without respiratory alkalosis. Anesth & Analg 52:522-528, 1973

3. Lawson NW, Butler GH III, Ray CT: Alkalosis and cardiac arrhythmias. Anesth & Analg 52: 951-964, 1973

4. Hoffman BF, Cranfield PF: The physiologic basis of cardiac arrhythmias. Am J Med 37:670-684, 1964

* * *

QUESTION: *. . . but for the (extremely rare) absolute contraindications, and (or) the "stonewall" resistance of an occasional patient to a regional, and (or) the lack of skill on part of the anesthesiologist necessitating it, is there any place for general anesthesia for adults in this day and age replete with knowledge of its (GA) dangers?*

MD, Illinois

ANSWER #1: Upon reflection of the many serious general anesthesia problems whose etiology and significance is unknown (malignant hyperthermia, "halothane hepatitis,"

trace elements of anesthetic agents, hyperkalemia-trauma-succinylcholine, abnormal pseudocholinesterases, irreversible pancuronium, "dual block," to enumerate a few), perhaps it is logical to seriously consider the relative merits of regional versus general anesthesia in adults.

It is well confirmed that properly administered peripheral nerve block for surgical anesthesia has the advantage over general anesthesia in that it does not upset general body physiology, e.g., depressed respiration, hypotension, cardiac arrhythmias, nausea, vomiting and regurgitation, and oliguria. By carrying pain relief into the postoperative period, peripheral nerve block decreases the need for narcotics, with their respiratory depression and complications. Because of the safety of regional anesthesia and the problems associated with general anesthesia, it would seem that, objectively, regional anesthesia should be chosen unless general anesthesia is specifically indicated.

Other than for the reasons enumerated in the question, I believe that general anesthesia is "indicated" for open-chest surgery, particularly cardiopulmonary bypass or coronary grafts. Patients with severe angina may be poor candidates for regional anesthesia because of the fine line between apprehension and (or) angina and depression from "sedation." According to Smith and Wollman,[1] general anesthesia seems to improve tolerance to cerebral ischemia, so that it might be preferred for carotid endarterectomy, although this is debated in vascular surgical circles.[2]

In summary, I would prefer to reword the question to say, "In this day and age with knowledge of general anesthesia dangers, does general anesthesia deserve the place it now holds in routine anesthesia practice (approximately 85% of the anesthesia is general)? The answer to that question is a resounding NO!!!

L. Donald Bridenbaugh, MD
Department of Anesthesiology
Mason Clinic
Seattle, Washington

REFERENCES

1. Smith AL, Wollman H: Cerebral blood flow and metabolism: effects of anesthetic drugs and techniques. Anesthesiology 36:391-396, 1972

2. Rainier WG, Guillen J, Bloomquist CD, et al: Carotid artery surgery: morbidity and mortality in 257 operations. Am J Surg 116:678-681, 1968

ANSWER #2: It is hardly appropriate to relegate general anesthesia to a category of being used only if regional anesthesia is contraindicated or impossible. Over the last 25 years, we have been fortunate in having had a variety of new general anesthetic agents developed. As a devotee of both regional and general anesthesia, I think we are fortunate to have such a wide repertoire of technics and agents available for our use. The anesthetic management of a patient should be tailored to fit the whole patient's needs, both surgical and psychological. With our extensive armamentarium of both general and regional anesthetic agents and technics, this is possible.

The questioner implies that the dangers of general anesthesia are greater than those of regional anesthesia. Documentation of this is lacking. Anecdotal reports can be found for each side of this question, but truly significant comparative studies have not been reported.

Operations on the upper extremities and distal to the diaphragm may be easily and relatively simply managed with regional anesthetic technics in the appropriate patient. Most other surgical procedures become a "tour de force" for regional anesthesia and are better managed with a general anesthetic.

Slightly over 50% of the anesthetics in the United States are administered by nurse anesthetists. It would be logistically impossible at this point to train nurses in the technics of regional anesthesia.

Finally, the patients in this country are accustomed to the concept of general anesthesia for surgical operations. This is a potent psychologic force which would be extremely difficult to overcome. To overcome this attitude, if this were desirable, would require a generation or more.

In summary, considering the operation to be performed, the mental attitude of the patient, the training and capabilities of the anesthetist, and the prejudices of our medical and surgical colleagues, there will always be room for both regional and general anesthesia. Only with this attitude are we able to make the anesthetic fit the patient's needs, rather than vice versa.

George E. Battit, MD
Department of Anesthesia
Massachusetts General Hospital
Boston, Massachusetts

The Effects of Doxapram on Cerebral Blood Flow and Peripheral Hemodynamics in the Anesthetized and Unanesthetized Goat

DAVID J. MILETICH, PhD*
ANTHONY D. IVANKOVICH, MD†
RONALD F. ALBRECHT, MD‡
ROGER F. BONNET, MD§
CHARLES R. REIMANN, MD‖
Chicago, Illinois**

The effects of doxapram on cerebral blood flow (CBF) and peripheral hemodynamics were evaluated in the goat after direct injection into the cerebral circulation and after peripheral IV administration. Doxapram injected centrally via the temporal artery, in doses too small to affect peripheral circulation, produced an immediate and prolonged decrease in CBF in both anesthetized and unanesthetized goats. The reduction in CBF was considered not to be due to changes in blood CO_2 concentration, since blood flow decreased immediately after injection and as reduction in CBF occurred in the absence of changes in blood CO_2.

Peripheral IV administration of doxapram in clinical doses to anesthetized and unanesthetized goats produced a biphasic cardiovascular response. Cerebral blood flow, cardiac output, blood pressure, and heart rate decreased abruptly, but with the exception of CBF, these parameters returned to or exceeded preinjection values within 30 seconds. Cerebral blood flow slowly returned to preinjection values (within 10 minutes) and, in the case of unanesthetized animals and anesthetized animals ventilated with room air, rose substantially above preinjection levels, reaching a peak 20 minutes after injection. The latter observation is thought to be a compensatory reaction to the reduction in CBF; it was not evident in anesthetized animals ventilated with 100% O_2.

REPORTS concerning the use of doxapram in both man and animals have indicated that this agent initiates cardiovascular alterations, characterized by moderate increases in blood pressure, heart rate, and cardiac output.[1-4] In most instances, cardiovascular changes due to doxapram administration appear tolerable in view of the clinical benefit from its use. However, it has been demonstrated that prolonged oral administration of doxapram to dogs produces petechial perivascular hemorrhages in brain tissue similar to the hemorrhage seen after ischemic hypoxia.[5]

Funderburk and associates[6] concluded that doxapram did not possess direct cerebral vasoactivity but influenced cerebral blood flow (CBF) secondary to its effect on respiration and blood gases. Contrary to this conclusion, we have observed that doxapram abruptly decreases CBF in both anesthetized and unanesthetized goats in a way not related to changes in blood gases. It

*Assistant Professor of Anesthesiology, Pritzker School of Medicine, The University of Chicago.

†Professor of Anesthesiology, Lincoln School of Medicine, University of Illinois.

‡Professor of Anesthesiology, Pritzker School of Medicine, The University of Chicago; Chairman, Department of Anesthesiology, Michael Reese Medical Center.

§Assistant Professor of Anesthesiology, Pritzker School of Medicine, The University of Chicago.

‖Research Associate, Department of Anesthesiology, Michael Reese Medical Center.

**Department of Anesthesiology, Michael Reese Medical Center, Chicago, Illinois 60616.

Paper received: 2/24/75
Accepted for publication: 8/5/75

was the purpose of this study, therefore, to simultaneously evaluate the effects of doxapram on CBF, blood gases, and cardiovascular hemodynamics, in order to gain a better understanding of the way in which doxapram influences cerebral blood flow.

METHODS

The studies were performed with a recently developed animal model for the continuous measurement of ipsilateral hemispheric CBF in the unanesthetized, unrestrained goat. We confirmed the validity of this approach for the study of CBF by the technic of radioactively labeled microspheres.[7] Anatomic description of the goat cerebral vasculature and methodology employed have been described elsewhere.[8,9]

Briefly, total blood flow to each hemisphere is provided by a single external carotid artery. The external carotid bifurcates extracranially, forming the lingual and internal maxillary arteries. Two major vessels, the ramus anastomoticus and arteria anastomotica, arise from the internal maxillary and enter the cranial vault, where they empty into the rete mirabile. Branches from the internal maxillary also supply blood to the extracerebral tissues via the buccinator, ethmoidal, and ophthalmic arteries. The rete mirabile consists of a compact network of intertwined, freely anastomosing arteries.

In the goat, a high degree of contralateral communication exists across the midline of the brain between each side of the rete. The vascular communication is so extensive that the two structures are virtually one. However, physiologic separation is maintained when the blood pressure in each side is equal. Abnormally low blood pressure in one rete incurs blood flow from the opposite rete, thus maintaining adequate blood flow to each hemisphere. In the goat, the vertebral arteries do not contribute to the cerebral blood supply.

Ten mature female goats weighing 30 to 40 kg were surgically prepared for study as described by Reimann's group.[9] Anesthesia was induced with mask-administered halothane after which the animal was intubated; artificial respiration was maintained by an Ohio respirator with 1.5% halothane in 100% O_2. An esophageal gastric tube was inserted to prevent vomiting and aspiration. A lateral incision was made along either the right or left mandible and a small portion of the mandible was removed to expose the internal maxillary, ramus anastomoticus, temporal, and dental arteries. Ligatures were placed around the internal maxillary distal to the ramus anastomoticus and on the temporal and dental arteries. Blood flow through the ophthalmic, ethmoidal, and buccinator arteries was obliterated by slowly injecting 1 to 2000 NIH units of thrombin in 0.5 ml of saline solution into the internal maxillary artery anterior to the site of ligation. The injected thrombin produced immediate clotting, as was evident by the appearance of thrombosed vessels in the sclera and postsurgical ipsilateral blindness. An electromagnetic flow probe was then placed around the internal maxillary. After this, under direct vision, a small catheter was placed into the temporal artery and advanced a distance of approximately 0.5 cm to the juncture of the temporal and maxillary arteries. Care was taken to avoid projection of the tip of the catheter into the maxillary artery. The catheter and leads from the electromagnetic flow probe were then externalized and secured to the goat's horn. The incision site was appropriately closed for proper healing.

Following this procedure, a right thoracotomy was performed and an electromagnetic flow probe was placed around the pulmonary artery for the measurement of cardiac output. Chronic femoral artery and venous catheters were then implanted. After completion of the surgical procedure, the animals were permitted to recover for at least a period of 1 week to 10 days before study.

Upon recovery, the animals were given doxapram either in small doses (4 mg) via the temporal artery catheter or IV via the femoral venous catheter in recommended clinical doses (1 mg/kg). The goats were studied in both the awake and halothane-anesthetized (usually 1.5%/100%) state. In the anesthetized animals, respiration was controlled by an Ohio anesthesia ventilator. Paralysis was induced when necessary by succinylcholine. Arterial blood samples were drawn at various intervals after doxapram injection for blood-gas analysis. Cerebral blood flow and cardiac output were continuously measured with a Statham electromagnetic flowmeter (model 2200).

Statistical significance of blood-gas changes following doxapram was determined by one-way analysis of variance. Significance of other parameters was evaluated under the null hypothesis, assuming an equal opportunity for no change, an increase, or a decrease in any parameter following doxapram.

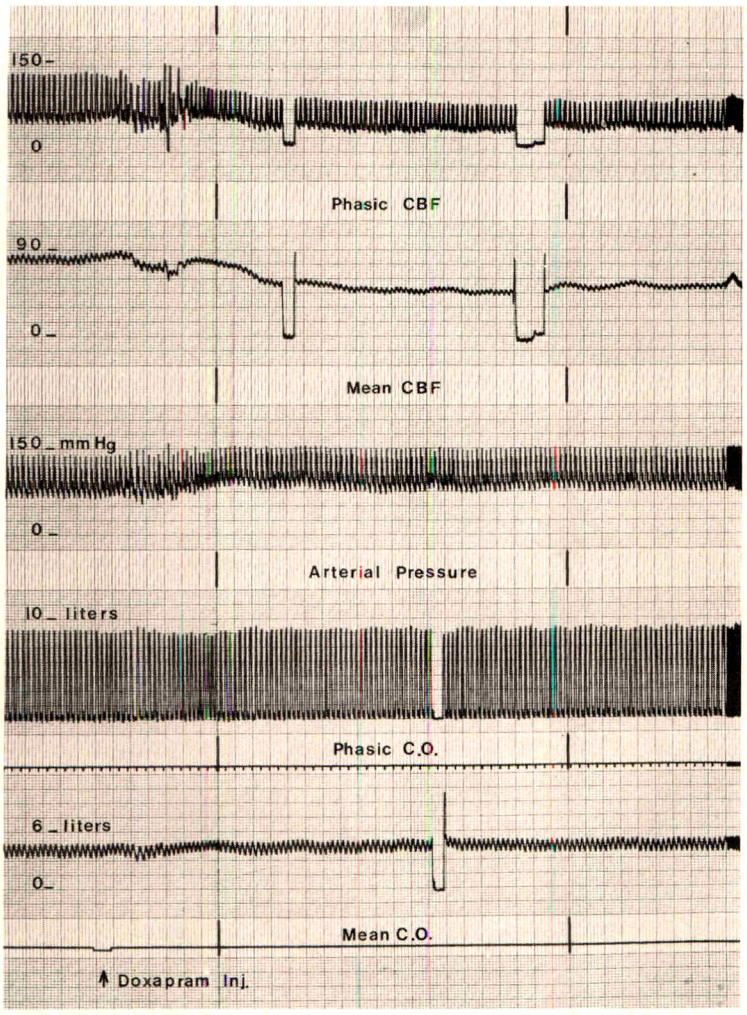


FIG 1. Typical cardiovascular changes in the unanesthetized goat after temporal artery injection of 4 mg of doxapram. Paper speed 2.5 mm/sec. ICBF = ipsilateral cerebral blood flow in ml/min, CO = cardiac output in L/min.

The probability of any situation occurring consecutively in multiple independent trials was therefore the product of its individual probability.

RESULTS

Figure 1 shows the effects of a bolus injection of doxapram (4 mg in 0.4 ml) via temporal artery catheter into the cerebral circulation of the unanesthetized goat. Within 6 seconds after injection, CBF began to decrease abruptly and arterial blood pressure and cardiac output rose slightly. These effects were typically seen in both unanesthetized and anesthetized animals. The doxapram-induced reduction in CBF was somewhat attenuated in the halothane-anesthetized animals (table 1). Halothane, a cerebrovascular vasodilator, may have opposed the vasoconstrictive effect of doxapram during anesthesia.

The hemodynamic alterations caused by a peripheral IV injection of doxapram (1 mg/kg) in an artificially ventilated, anesthetized goat are shown in figure 2 and summarized in table 2. Immediately after injection, CBF, arterial blood pressure, heart rate, and cardiac output dropped sharply. Generally, all parameters returned to or exceeded preinjection values after 3 minutes except for CBF, which in every case remained below preinjection values for a considerably longer period (6.2 ± 2.4 minutes; mean ± SD). Blood gases, particularly CO_2, did not fluctuate significantly during this period (table 3). Intravenous administration of doxapram (1 mg/kg) produced similar

TABLE 1
Reduction in Ipsilateral Cerebral Blood Flow After Central Administration of Doxapram (4 mg) in the Anesthetized and Unanesthetized Goat

	Anesthetized	Unanesthetized
Control ipsilateral CBF	93 ± 18 ml/min	75 ± 13 ml/min
30 sec (post-injection)	74 ± 6*	67 ± 14*
1 min (post-injection)	72 ± 6*	62 ± 11*

*Mean % ± SD of control values, $p < 0.05$; n = 18.

hemodynamic changes in unanesthetized and anesthetized goats (table 2).

In addition to the "early" cardiovascular changes seen after IV doxapram administration, within 10 minutes postinjection, CBF was seen to increase above preinjection values in unanesthetized animals (fig 3A) and in anesthetized animals ventilated with room air (fig 3B). This increase was generally seen 15 to 20 minutes after injection and may have been a compensatory response to the prior CBF reduction. Anesthetized animals ventilated with 100% O_2 exhibited only a slight increase in CBF (fig 3C). In unanesthetized animals, blood CO_2 concentrations at 20 minutes were lower than preinjection levels and therefore could not account for the elevated CBF seen in these animals (table 4).

DISCUSSION

In this study, the hemodynamic effects of IV doxapram and doxapram injected directly into the cerebral circulation of anesthetized and unanesthetized animals were evaluated. Immediately after injection, arterial blood pressure, cardiac output, heart rate, and CBF decreased abruptly. Approximately 30 seconds after injection, these parameters returned to preinjection values and in

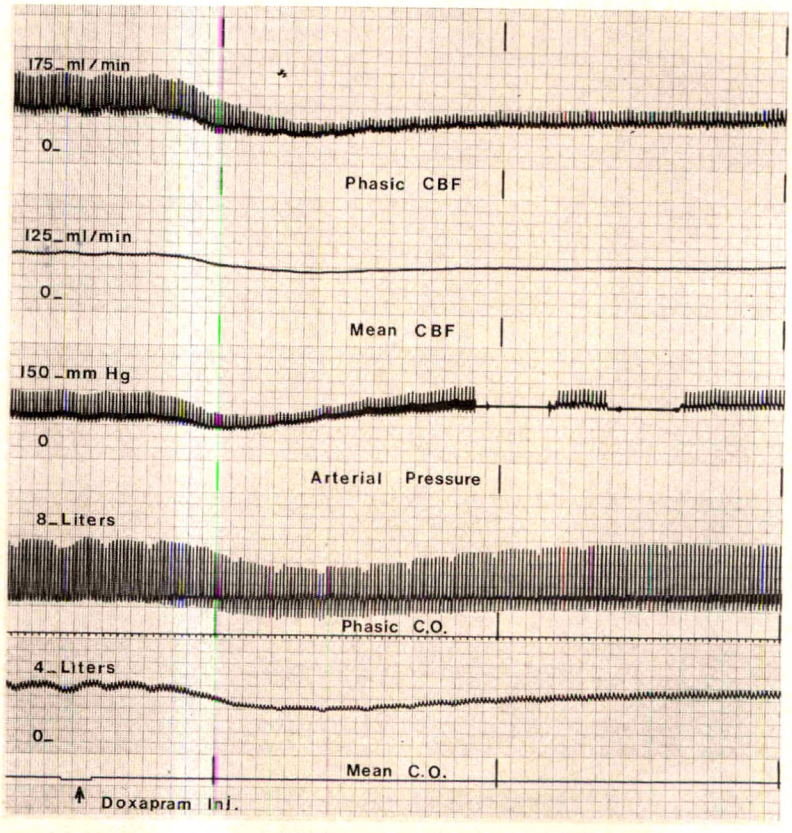


FIG 2. Typical cardiovascular changes in the anesthetized goat after IV injection of doxapram (1 mg/kg). Paper speed 2.5 mm/sec. ICBF = ipsilateral CBF in ml/min, CO = cardiac output in L/min. Interruptions in blood pressure tracing due to blood-gas determination.

TABLE 2
Cardiovascular Effects of IV Doxapram Injection (1 mg/kg) in the Anesthetized and Unanesthetized Goat

	Control values	30 seconds	1-2 minutes	5 minutes	20 minutes
			Anesthetized		
Ipsilateral CBF	94 ± 12 ml/min	71 ± 8*†	70 ± 6†	86 ± 8†	97 ± 12
Cardiac output	4.36 ± 1.9 L/min	58 ± 20†	87 ± 10†	103 ± 7	106 ± 5
Heart rate	115 ± 22 min	78 ± 13†	83 ± 9†	97 ± 5	106 ± 5
Mean arterial blood pressure	94 ± 7 torr	140 ± 25†	129 ± 9†	119 ± 13	109 ± 7
			Unanesthetized		
Ipsilateral CBF	78 ± 10 ml/min	—	75 ± 8†	—	152 ± 21†
Cardiac output	5.22 ± 2.1 L/min	—	77 ± 8†	—	110 ± 3†
Heart rate	112 ± 8 min	—	87 ± 3†	—	99 ± 8
Mean arterial blood pressure	94 ± 9 torr	—	131 ± 16†	—	103 ± 7

*Values represent mean % ± SD of control.
†Difference statistically significant from control values, $p<0.05$, n = 10.

TABLE 3
Arterial Blood Gas and pH Values After IV Doxapram Injection (1 mg/kg) in the Anesthetized Goat with Controlled Ventilation

	Control	1 minute	5 minutes
P_{CO_2}, torr	34.3 ± 6.2*	31.7 ± 3.7†	34.8 ± 2.2
P_{O_2}, torr	380 ± 18	385 ± 12	385 ± 14
pH	7.48 ± 0.06	7.47 ± 0.09	7.48 ± 0.07

*Values represent mean ± SD, n = 10.
†No statistical difference.

some instances rose above control values, with the exception of cerebral blood flow, which returned to preinjection levels after several minutes. These changes in CBF were not due to fluctuations in blood gases, since respiration was controlled and CO_2 levels held constant. Peripheral cardiovascular changes may have contributed to the early decrease in CBF, but peripheral hemodynamic parameters returned to normal or greater values long before cerebral blood flow. In addition, small doses of doxapram injected directly into the cerebral circulation via the temporal artery produced reductions in CBF identical with those seen with clinical IV doses, but without peripheral cardiovascular manifestations.

The effects of doxapram on CBF and peripheral hemodynamics in the unanesthetized animal were similar to those seen in anesthetized animals with one important exception. In the unanesthetized animal, CBF exhibited a protracted biphasic response. Immediately after the period of reduced flow, CBF rose gradually until above the preinjection level. It remained elevated for as long as 30 minutes in some instances before returning to predoxapram levels. This pattern of blood flow is suggestive of the hyperemic response seen in tissues and organs following O_2 deprivation during a period of reduced flow.

Anesthetized animals may not have responded in this fashion because they were ventilated with 100% O_2 and were not subjected to hypoxia as a result of the reduced cerebral blood flow. Supporting this hypothesis is the observation that CBF in anesthetized animals ventilated with room air behaved much as that in unanesthetized animals after doxapram injection. That these changes in CBF were not the result of changes in arterial blood CO_2 is evident from the fact that when CBF was elevated, CO_2 concentrations were below predoxapram values. However, it is possible that brain tissue concentrations of CO_2 built up during the period of reduced CBF could have elicited the subsequent cerebral vasodilation.

It is not possible from the data presented

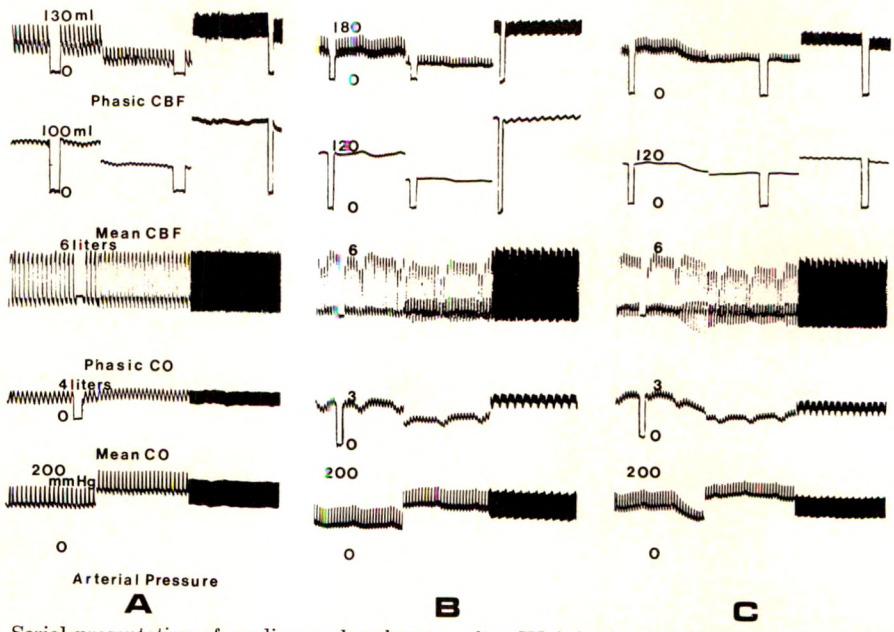


FIG 3. Serial presentation of cardiovascular changes after IV injection of doxapram (1 mg/kg). First panel in each series represents preinjection values; 2nd panel, the lowest point of CBF decrease (2 to 3 min after injection); 3rd panel, the highest point in CBF increase (15 to 20 min after injection). A, unanesthetized goat; B, anesthetized goat ventilated with room air; C, anesthetized goat ventilated with 100% O_2. Paper speed 2.5 mm/sec in 1st two panels of each series and 0.4 mm/sec in 3rd panel of each series. ICBF = ipsilateral CBF in ml/min, CO = cardiac output in L/min.

TABLE 4
Arterial Blood Gas and pH Values After IV Doxapram Injection (1 mg/kg) in the Unanesthetized Goat

	Control	20 minutes
P_{CO_2}, torr	36.05 ± 3.22*	31.9 ± 3.93†
P_{O_2}, torr	92 ± 14	104 ± 16†
pH	7.46 ± 0.02	7.51 ± 0.04†

*Values represent mean ± SD, n = 10.
†No statistical difference.

here to distinguish the mechanism or mechanisms by which doxapram produced peripheral cardiovascular depression and stimulation in both anesthetized and unanesthetized animals. A recent study has shown that doxapram is a nonselective medullary stimulant.[10] Perhaps doxapram stimulates cardioregulatory regions in the brain as well as in areas involved in respiration. However, arguing against this is the observation that small doses injected directly into the cerebral circulation produced only mild peripheral hemodynamic changes.

The findings of this study directly contradict those previously reported,[6] that doxapram produces cerebral vasoconstriction indirectly by inducing hyperventilation and lowering blood CO_2 concentrations. Our data indicate that doxapram constricts the cerebral vasculature in a way unrelated to changes in blood gases and peripheral hemodynamics. It should be noted that the former study was based upon observations made in only two animals, and that blood flow in only a small area of the cortex of each animal was evaluated, factors that place severe restraints upon interpretation of the results. In addition, species difference could account for the variance of results seen between our data and those previously reported.

The clinical significance of the effects of doxapram in the goat is at this point speculative. If CBF is reduced in humans when doxapram is administered, there may be a greater amount of O_2 extracted from each milliliter of blood perfusing the brain and no change in net O_2 uptake or availability. There is, however, a limit to the ability of the brain to compensate for decreases in perfusion by increased O_2 extraction.[11] It is possible that, in some patients, such a decrease in CBF will result in a critical decrease in available O_2, particularly in marginally oxygenated or anemic patients.

REFERENCES

1. Wasserman AJ, Richardson DW: Human cardiopulmonary effects of doxapram, a respiratory stimulant. Clin Pharmacol Ther 4:321-325, 1963

2. Miller MJ, Fiedler HJ: Pharmacologic effects of doxapram in the awake human. J Am Geriatr Soc 13:160-165, 1965

3. Huffington P, Craythorne NWB: Effect of doxapram on heart rhythm during anesthesia in dog and man. Anesth & Analg 45:558-563, 1966

4. Insinna F, Natale E, Tornartore C: Experimental observations on some cerebral, cardiovascular, and respiratory effects of doxapram hydrochloride. La Clinica 28:317-324, 1968

5. Woodward G, Ward JW, Mann GT: Safety evaluation of the respiratory stimulant doxapram HCl by oral and parenteral administration to laboratory animals. Toxicol Appl Pharmacol 6:364-369, 1964

6. Funderburk WH, Oliver KL, Ward JW: Modification of cerebral blood flow in dogs with doxapram hydrochloride. Toxicol Appl Pharmacol 13:67-75, 1968

7. Miletich DJ, Ivankovich AD, Albrecht RF: Cerebral hemodynamics following internal maxillary artery ligation in the goat. J Appl Physiol 38:942-945, 1975

8. Daniel PM, Dawes JDK, Prichard MML: Studies of the carotid rete and its associated arteries. Philos Trans 237:173-208, 1953

9. Reimann CL, Lluch S, Glick G: Development and evaluation of an experimental model for the study of cerebral circulation in the unanesthetized goat. Stroke 3:322-328, 1972

10. Hirsch K, Wang SE: Selective respiratory stimulating action of doxapram compared to phenyleneterazol. J Pharmacol Exp Ther 189:1-11, 1974

11. Eckenhoff JE: The cerebral circulation. Postgrad Med J 50:566-567, 1974

BLOOD GAS VALUES Gas tensions in blood withdrawn from a Swan-Ganz catheter in the proximal pulmonary artery and wedge position were compared. Blood gas tensions from the wedge position, but with the balloon deflated, varied greatly. A high percentage of these samples were similar to the mixed venous (pulmonary artery) samples reflecting the high incidence of nonventilated lung areas in critically ill patients. This finding also emphasizes the fact that a Swan-Ganz catheter may be properly placed but unsaturated blood still obtained when used in patients with atelectasis. The high O_2 tension in samples from the wedge position may result from admixture of pulmonary capillary blood during sample withdrawal and/or diffusion of alveolar gases through the walls of small pulmonary arteries. Using this false high O_2 partial pressure would result in errors in calculated O_2 content used in the Fick determination of cardiac output and right-to-left shunt. Blood samples from Swan-Ganz catheters should be withdrawn slowly (3 ml/min) and results interpreted cautiously. Criterion for proper wedge position should no longer include aspiration of saturated blood especially in patients with lung disease. *(Suter PM, Lindauer JM, Fairley HB et al: Errors in data derived from pulmonary artery blood gas values. Crit Care Med 3:175-181, 1975)*

Etomidate: An Ultrashort-Acting Nonbarbiturate Agent for Anesthesia Induction

JOHN M. GOODING, DO*
GUENTER CORSSEN, MD†
Birmingham, Alabama‡

Clinical evaluation of etomidate, an ultrashort-acting nonbarbiturate hypnotic agent, shows it to be useful for anesthetic induction in adults. It produces sleep in 1 arm-brain circulation time, metabolites apparently peaking at 7 minutes postinjection. Cardiovascular and respiratory systems appear minimally affected and there is no indication of organ toxicity or other biochemical or hematologic drug-induced disturbances. Moderate pain on injection at some sites and transient myoclonia were the principal disadvantages observed.

INDUCTION of general anesthesia involves 2 personal viewpoints, not necessarily conflicting: The patient wants to go to sleep comfortably—what matters most to him is a rapid and pleasant induction. The anesthesiologist, too, values the advantage of speedy onset of sleep, but his first concern is for the safety of his patient with respect to the drug used.

Because the hypnotic agents now available are often associated with significant adverse effects, the search continues for the "ideal" nonbarbiturate drug whose duration of action is ultrashort. Recently, Janssen,§ studying a series of compounds related to imidazole-carboxylate, found the ethyl-methylbenzyl-imidazole-carboxylate, etomidate, to offer distinct advantages over other induction agents tested.

Etomidate (figure) is water-soluble and is provided as the sulfate. It produces sleep in a single arm-brain circulation time. Since its breakdown to inactive metabolites takes place through hydrolysis, its short duration of action does not depend solely on redistribution. The hydrolysis, affecting the ethyl-ester side chain takes place in both the blood and the liver.[1]§ Metabolites reach a peak 7 minutes after injection and are inert

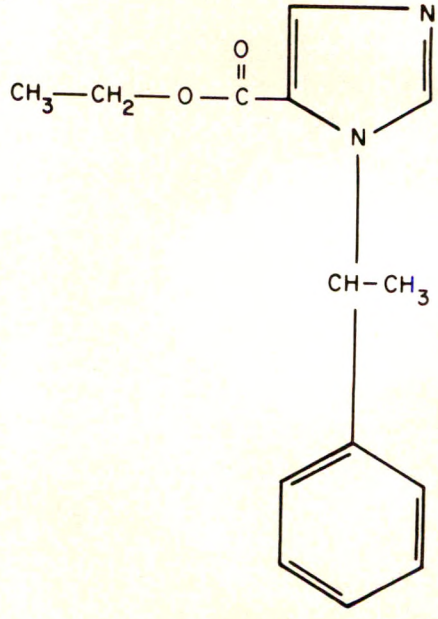


FIGURE. Chemical structure of etomidate (ethyl-1-methylbenzyl-imidazole-5-carboxylate; R7405; R26490).

§Janssen Pharmaceutica, Research Laboratories, B-2340, Beerse, Belgium.

*Assistant Professor.
†Professor and Chairman.
‡Department of Anesthesiology, University of Alabama School of Medicine, Birmingham, Alabama 35294.

Paper received: 12/1/75
Accepted for publication: 1/6/76

with respect to sedative properties.[1*] The cardiovascular and respiratory systems appear minimally affected, and there is no indication of organ toxicity or other biochemical or hematologic drug-induced disturbances.[1*] Etomidate does not cause detectable histamine release.[2]

Published reports[1,3,4] on the clinical use of etomidate as an intravenous induction agent showed enough pharmacologic advantages to warrant our further clinical investigation in human volunteers.

METHODS

The series included 48 male and female surgical patients, aged 18 to 75 (mean 45.9) years, in a predetermined randomized order of 3 types of premedicants, 2 hypnotics, and 2 speeds of injection. For each case informed consent was obtained. Premedication, administered intramuscularly 15 to 45 minutes before induction of anesthesia, consisted of 0.5 mg of atropine, 0.1 mg of fentanyl with 0.5 mg of atropine or 10 mg of diazepam with 0.5 mg of atropine. Anesthesia was induced with sodium thiopental (4 mg/kg IV) or etomidate (0.3 mg/kg IV). Speed of injection was either 30 or 60 seconds, and the injection site was either the dorsum of the hand or the antecubital fossa. Concurrent medications were noted but not discontinued.

During administration of the induction hypnotics and for 3 minutes afterward, the following determinations were recorded: systolic and diastolic blood pressure (inflatable cuff), heart rate (ECG), hypoventilation or apnea, involuntary movements, and pain at the injection site. Each patient was observed during the operation and immediately afterward, and follow-up visits were made 24 and 48 hours after operation. All values were subjected to computerized statistical analysis.

RESULTS

Systolic blood pressure after thiopental induction was reduced by 15 torr and after etomidate by 5 torr. No change in diastolic pressure was noted with either hypnotic agent. Heart rate increased 6 beats per minute after thiopental but did not change with etomidate. The cardiovascular differences were not statistically significant.

With etomidate, slight myoclonia developed in 25% of the patients and severe myoclonia in 8% (significance borderline); all were of brief duration. There was no instance of myoclonia among patients receiving thiopental, and no severe myoclonia among etomidate subjects who had received diazepam or fentanyl as premedication.

Pain on injection was noted in 37% of the etomidate group, all of whom had the injection site on the dorsum of the hand; no patient experienced pain when an antecubital vein was used. The incidence of pain was higher at the 60-second injection speed than at 30 seconds. With respect to premedication, 50% of patients receiving atropine alone experienced venous pain, whereas the incidence was 38% with fentanyl and atropine and 25% with diazepam and atropine. In 1 patient, chemical phlebitis followed etomidate induction; the condition lasted less than 24 hours. No patient receiving thiopental experienced pain on injection or developed phlebitis.

With etomidate induction, hypoventilation occurred in 25% of the patients and transient apnea was noted in 16%. Persistent apnea occurred only following thiopental (96%) necessitating controlled ventilation and subsequent intubation. Neither the speed of injection nor the type of premedication showed any correlation with respiratory depression.

DISCUSSION

Etomidate appears to meet many of the requirements for an optimal induction agent, particularly with respect to duration of action and effects on cardiovascular function.

Janssen* and others[1,3-5] have reported the heart rate to be not affected, or increased only slightly and for a short time. Systemic vascular resistance appears to be reduced and cardiac output and stroke volume increased.[3,4] Myocardial O_2 consumption is reduced;[3,4] myocardial contractility is not significantly impaired.[5] In our series, there was no significant difference in cardiovascular function with either hypnotic agent used. Systolic and diastolic blood pressure remained stable; heart rate increased slightly with thiopental but not with etomidate.

One significant adverse effect of etomidate is the occurrence of involuntary movements. The origin of such motion is thought to be disinhibition of uncoordinated brainstem

*Janssen Pharmaceutica.

activity,[6] the incidence having been reported to be as high as 25%.[1] Rarely, however, are the involuntary movements intense enough to be troublesome. In one study involving 100 cases undergoing etomidate induction, only 4 instances of involuntary movements were of clinical importance, and these were transient.[1] Marked myoclonia has been precipitated by physical contact with the patient during drug administration,[1] the incidence of myoclonia reportedly being reduced by premedication with diazepam and the use of higher doses of etomidate.

None of the instances of severe myoclonia occurred in patients who had received diazepam or fentanyl premedication, and in no case did the involuntary movements persist beyond the 1st minute after injection.

Another reported disadvantage of etomidate is pain at the site of injection, particularly in the dorsum of the hand.[1] The importance of the injection site was confirmed in our series; pain did not occur when a proximal vein was used. It is intriguing that the incidence of such pain was lower with diazepam than with fentanyl premedication. Our negligible incidence of phlebitis is in accord with findings elsewhere.[1]

Being a purely hynotic agent, etomidate lacks analgesic properties. When pain is present or anticipated, this agent should be accompanied by an appropriate analgesic drug.

Complementing the advantage of cardiovascular stability is the drug's short duration of action—resulting, as noted by Janssen and others,[1]* from hydrolysis of its ethyl-ester side chain. In one published study,[6] subjects were alert and able to talk 8 minutes after injection. Sedation may be prolonged with higher doses, repeated doses, or with long-acting premedication.

Induction is as rapid as with thiopental.[1] Maximum brain levels are said to be reached within 1 minute after injection.*

Respiration is affected but not to the extremes commonly seen with thiobarbiturates. Transient hypoventilation is usually the most common adverse respiratory effect. Short-lasting apnea has been reported in as many as 12% of cases,[1] with the subjects resuming spontaneous breathing within 90 seconds.

*Janssen Pharmaceutica.

The apnea noted in 16% of our patients receiving etomidate was transient, spontaneous ventilation returning within 2 minutes. Since the subjects were allowed to breathe O_2 before and during induction, ventilatory assistance was not required. Only after thiopental was controlled ventilation and subsequent intubation necessary. Transient hypoventilation was more common in the etomidate group, affecting 25% of the patients. The speed of injection and type of premedication did not affect the incidence of respiratory depression with either hypnotic.

Since etomidate has not been associated with detectable release of histamine,[2] reactions such as profound hypotension, urticaria, or bronchospasm should not occur as clinical problems.

Patients described etomidate induction as pleasant, and there appeared to be adequate amnesia. There were no reports of "hangover" or headache. Etomidate induction appears to be compatible with any type of maintenance anesthesia. No instances of hallucinations or psychotic experiences occurred during the awakening period.

In our series, etomidate was well accepted by both patients and anesthesiologists. In view of its pharmacologic properties, one might expect its beneficial use in emergency and cardiovascular surgery, in 1-day surgery and short surgical procedures, in high-risk patients, in patients with anticipated airway problems, and in anesthesia for diagnostic and elective procedures, such as cardioversion. Further study is needed to establish the role of this agent in these and other conditions involving the induction of other types of general anesthesia than those described herein.

ACKNOWLEDGMENT

The authors wish to express their appreciation to Dr. David C. Hurst, Professor and Chairman of the Department of Biostatistics, for his valuable help.

REFERENCES

1. Morgan M, Lumley J, Whitwam J: Etomidate a new water-soluble nonbarbiturate intravenous induction agent. Lancet 955-956, 1975

2. Doenicke A, Lorenz W, Beigl R, et al: Histamine release after intravenous application of short acting hypnotics. Br J Anaesth 45:1097-1104, 1973

3. Kettler D, Sonntag H, Donath U, et al: Hemodynamics, myocardial mechanics, oxygen

requirements and oxygen consumption of the human heart during etomidate induction into anaesthesia. Anaesthesist 23:116-121, 1974

4. Weymar A, Eigenheer F, Gethmann JW, et al: Experimental animal studies on the effects of etomidate (R26.490 sulfate) on the circulation and myocardial oxygen supply. Anaesthesist 23:150-157, 1974

5. Doenicke A, Gabanyi D, Lemce H, et al: Circulatory dynamics and myocardial function following three short-acting IV hypnotics: etomidate, propanidid, methohexital. Anaesthesist 23:108-115, 1974

6. Doenicke A, Kugler J, Penzel G, et al: Brain function and safety after IV use of etomidate, a new barbiturate-free hypnotic. Anaesthesist 22:357-366, 1973

ENDOTRACHEAL ANTIBIOTICS Gentamicin or aminosidin plus polymyxin B was administered into the tracheas of patients with tracheostomies 3 times daily. Positive cultures of bronchial secretions occurred in 47.7 and 53.1% of patients respectively. However, there was a difference in the nature of the offending organism in the 2 groups. Klebsiella was recovered from 28.8% of the specimens obtained from patients who received gentamicin and in only 5.9% of those from aminosidin-polymyxin treated patients. Pseudomonas aeruginosa and pneumococci were found more frequently in the aminosidin/polymyxin than gentamicin group but the differences were not statistically different. The administration of aminosidin/polymyxin was associated with a transient irritative cough in some patients. *(Klastersky J, Hensgens C, Noterman J et al: Endotracheal antibiotics for the prevention of tracheobronchial infections in tracheotomized unconscious patients. A comparative study of gentamicin and aminosidin-polymyxin B combination. Chest 68:302-306, 1975)*

PULMONARY EDEMA Thirty-seven critically ill patients with suspected hypovolemia received an intravenous fluid challenge. Twenty-one patients receiving primarily colloid solutions manifested slightly elevated left ventricular filling pressures but normal plasma colloid osmotic pressures. None of these patients developed pulmonary edema. Eleven patients receiving primarily crystalloid solutions developed pulmonary edema in association with normal left ventricular filling pressures but reduced colloid osmotic pressures. Treatment with furosemide was associated with a clearing of pulmonary edema and normalization of colloid osmotic pressure. The other 5 patients developing pulmonary edema received colloids and developed only elevated filling pressures. These observations emphasize that pulmonary edema may occur in the presence of a normal left ventricular filling pressure especially if large volume crystalloid infusion lowers colloid osmotic pressure. When large volumes of fluid are required it is safer to administer colloids which tend to maintain the colloid osmotic pressure. *(Stein L, Beraud JJ, Morissette M et al: Pulmonary edema during volume infusion. Cir 52:483-489, 1975)*

The Influence of Suction Catheter Tip Design on Tracheobronchial Trauma and Fluid Aspiration Efficiency

WILLIAM J. LINK, PhD*
EDMUND E. SPAETH, PhD†
WILLIAM M. WAHLE, MD‡
WILLIAM PENNY, MS§
JOHN L. GLOVER, MD‖

The suctioning efficiency and trauma-producing characteristics of five commercially available tracheobronchial suction catheters (Pharmaseal Tri-Flo, NCC Gentle-Flo, Argyle Aero-Flo, Argyle Dual Side-Hole, and Pharmaseal Whistle-Tip) were experimentally evaluated in anesthetized healthy dogs. The tendency of catheters to invaginate or "grab" tracheobronchial mucosa was observed with a bronchofiberscope during suctioning. Mucosal grabbing was seldom seen even at high (>300 torr) vacuum levels with the catheter tip in the trachea. All catheters were observed to invaginate mucosa in lobar and segmental bronchi, with the frequency of grabbing being a function of airway anatomy, airway size, catheter orientation, tip design, and vacuum level. Catheters with multiple side-holes appeared to invaginate mucosa less frequently than the single side-hole catheter.

Repeated suctioning of anesthetized healthy dogs followed by tracheobronchial excision, gross observation, and histologic examination of mucosal tissue biopsies demonstrated significant differences in the frequency and severity of lesions caused by the tracheobronchial suction procedure. All catheters were observed to damage airway lining, the damage related to multiple side-hole catheters appearing to be associated entirely with the act of catheter insertion and not with the application of vacuum. Only the Whistle-Tip design produced measurable damage beyond that related to catheter insertion.

The average tip-suctioning effectiveness for each catheter, determined *in vitro* by aspirating a thin, uniform layer of simulated mucus, was found to be significantly higher for the Tri-Flo and Whistle-Tip catheters than the others, the Aero-Flo being least effective. Preliminary attempts to demonstrate this difference in suctioning effectiveness by comparing the performance of the catheters which displayed the highest and lowest tip suction effectiveness in a standardized clinical suctioning procedure revealed no significant difference in the percentage of mucus removed by either catheter. Additional studies should clarify this apparent contradiction.

TRACHEOBRONCHIAL suction is a common and necessary procedure in patients whose ability to clear tracheobronchial secretions is impaired. In the past 2 decades, the procedures used in tracheobronchial aspiration have been given considerable attention, yielding several revisons in recommended technics. Aseptic technic to reduce bacteriologic colonization and cross-contamination in the trachea, moderate vacuum levels and limited duration of suctioning to reduce hypoxia, and the use of smooth, flexible catheters with vacuum control vents and side-holes near the tip to minimize trauma to tracheal and bronchial mucosa have been suggested.[1-3]

*Assistant Professor, Department of Surgery, Marion County General Hospital, Indiana University Medical Center, Indianapolis, Indiana 46202.

†Director, Hospital Group, Applied Research, American Hospital Supply Corporation, Glendale, California.

‡Assistant Professor, Department of Pathology, Marion County General Hospital, Indiana University Medical Center.

§Senior Analyst, Hospital Group, Applied Research, American Hospital Supply Corporation.

‖Professor, Department of Surgery, Marion County General Hospital, Indiana University Medical Center.

Paper received: 4/21/75

Accepted for publication: 8/11/75

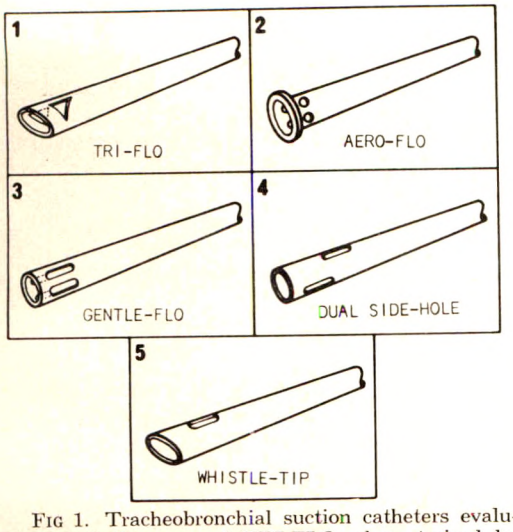


FIG 1. Tracheobronchial suction catheters evaluated: (1) Pharmaseal TRI-FLO, characterized by 2 triangular side-holes, offset from the center line and close to the beveled catheter tip. (2) Argyle AERO-FLO,characterized by 4 small, round side-holes near the expanded tip. (3) National Catheter Corporation GENTLE-FLO, characterized by 4 oval side-holes close to the tip. (4) Argyle Dual Side-Hole, characterized by 2 large side-holes somewhat removed from the tip. (5) Pharmaseal WHISTLE-TIP, characterized by a single side-hole.

Recently, Sackner and associates[4] reported no gross abnormalities in the distal trachea of dogs suctioned with the new Argyle Aero-Flo suction catheters (which supports an expanded tip and 4 small side-holes near the tip) while all dogs suctioned with conventional "whistle-tip" (single side-hole catheters) displayed gross changes, including edema, hyperemia, mucosal ulceration, and hemorrhage throughout the mucosa of the tracheobronchial tree. The Aero-Flo catheter has accordingly been referred to as "atraumatic."

Since this reported breakthrough in suction catheter tip design, two other suction catheters designed to reduce tracheobronchial trauma during aspiration have also become available. Unlike the conventional whistle-tip suction catheter with a single side-hole, the new low-trauma catheters have multiple side-holes of varying number and configuration. The multiple side-holes are significant in that the probability of occlusion of all the holes simultaneously during suctioning is decreased, reducing the opportunity for invaginating or "grabbing" the mucosa. However, by increasing the number of side-holes, there is also the possibility of reducing the suctioning effectiveness of the catheter as a result of excessive venting. Thus it bcomes important to determine not only the extent to which these new catheters reduce trauma, but also the extent to which their suctioning efficiency may be altered as a result.

In this study a variety of *in vitro* and *in vivo* animal experiments as well as preliminary clinical tests were used to investigate the tendency to induce tracheobronchial damage and the suctioning effectiveness of five types of catheters.

METHODS

Catheters evaluated included (fig 1): (1) Pharmaseal Tri-Flo, (2) National Catheter Corporation Gentle-Flo, (3) Argyle Aero-Flo, (4) Argyle Dual Side-Hole, and (5) Pharmaseal Whistle-Tip. The first three catheters are sold as either "atraumatic" or low-trauma catheters. The Pharmaseal Whistle-Tip was considered representative of the general class of single side-hole catheters. All catheters tested were size 14 French and were made of clear, flexible plastic material.

TRACHEOBRONCHIAL DAMAGE

Invagination of Mucosa.—The tendency of each catheter to invaginate tracheal and bronchial mucosa was observed visually by fiberoptic bronchoscopy in healthy mongrel dogs anesthetized with sodium pentobarbital (30 mg/kg) while varying the suctioning vacuum level (Gomco Aspirator, Model 930) over a range of 80 to 630 torr. This procedure was performed by two individuals, one regulating the vacuum level and the other noting the catheter performance while being unaware of the vacuum level. All five catheters were observed over the entire vacuum range in each of three animals, with a different observer for each animal.

Tracheobronchial Trauma. — To determine the extent of trauma accompanying extensive suctioning, a total of 42 healthy mongrel dogs weighing 11 to 18 kg were anesthetized with sodium pentobarbital, intubated, and maintained on spontaneous respiration. Following anesthesia and intubation, the mucosa of the tracheobronchial tree was observed with the bronchofiberscope.

Catheters were then fully inserted into the tracheobronchial tree, withdrawn slightly, and then 180 torr vacuum was applied for 3 to 5 seconds while steadily rotating

and withdrawing the catheter. The catheters, irrigated with water and lightly lubricated with mineral oil between each pass, were passed at 3-minute intervals over a 4-hour period, with a total of 80 passes in each animal. At the end of the procedure, the tracheobronchial tree was again observed with the bronchofiberscope, 35-mm color photographs being taken where lesions were present. The animals were then killed with an overdose of sodium pentobarbital, the thorax was opened, and the location of the tip of the endotracheal tube noted prior to excising the lungs. The airways were opened to the lobar bronchi, gross observations were made, and color photographs were taken. The tracheobronchial tree was then sectioned for histologic examination at a minimum of five locations: (1) 12.7 cm above the carina, (2) 7.6 cm above the carina, (3) 2.54 cm above the carina, (4) right mainstem bronchus, and (5) left mainstem bronchus. In addition, if specific gross lesions were noted, they were also sectioned for histologic examination. The microscopic slides were routinely prepared and the identity of the specimens was not revealed to the pathologist prior to examination.

The animals used in the trauma study fall into 8 groups, one group for each of the 5 catheters being tested and 3 control groups (table 1). To differentiate suction-related damage from damage due to merely inserting the catheters, catheters were passed in 4 dogs in the previously described manner except that no vacuum was applied. In addition, 2 animals served as "bronchofiberscope controls," in that they were handled as previously described while passing only the bronchofiberscope (no catheters), and 5 animals were "clean controls," in that they were anesthetized, intubated, and maintained under anesthesia for 4 hours without inserting catheters or bronchofiberscope into the tracheobronchial tree.

TABLE 1
Dogs Used in Tracheobronchial Damage Study Following Suctioning by Various Catheters

Group	Number of dogs	Catheter type	Number of catheter passes/animal	Bronchofiberscope, number of passes/animal	Vacuum applied
1	9	Tri-Flo	80	2	Yes
2	5	Aero-Flo	80	2	Yes
3	5	Gentle-Flo	80	2	Yes
4	4	Dual Side-Hole	80	2	Yes
5	8	Whistle-Tip	80	2	Yes
6	4	*	80	0	No
7	2	—	0	2	—
8	5	—	0	0	—

*One animal each—Tri-Flo, Aero-Flo, Dual Side-Hole and Whistle-Tip.

CATHETER SUCTION EFFICIENCY

This was evaluated by three approaches: (1) by aspirating viscous lubricating gel from the tracheobronchial tree in dogs (*in vivo* and *in vitro*), (2) by suctioning lubricating gel of varying viscosity and film thickness in a horizontal trough, and (3) in clinical trials.

Animal Studies.—Five dogs were anesthetized with sodium pentobarbital, intubated, maintained on spontaneous respiration, and the location of the carina with respect to the endotracheal tube established via bronchofiberoscopy. To simulate a film of mucus, a measured amount of lubricating gel (viscosity equal to 550 poise) was dispersed at given locations along the trachea by injecting it through a size 14 French catheter. Though various protocols were tried, a typical procedure was to inject a total of 3 ml of gel in boluses of ¼ ml at 1.27 cm intervals, starting 2.54 cm above the carina. A catheter was then passed to the level of the carina and uniformly withdrawn while applying vacuum (180 torr) for 5 seconds.

The amount of gel removed was weighed and the excess gel in the trachea was aspirated prior to the next catheter insertion. This procedure was repeated 10 times with each catheter. The animal was then killed, the lungs were removed from the thorax, and the dorsal surface of the trachea was longitudinally transected. The lungs were placed on a flat surface, with the trachea being slightly elevated (approximately 15° angle), lubricating gel was placed in the trachea, and the suctioning procedure was repeated as described above.

Catheter Tip Suction Efficiency.—Tracheobronchial secretions adhere to the wall of the tracheobronchial tree, forming a relatively thin film of variable thickness. Also, the inserted catheter lies with its axis essentially parallel to the airway wall. Hence, an

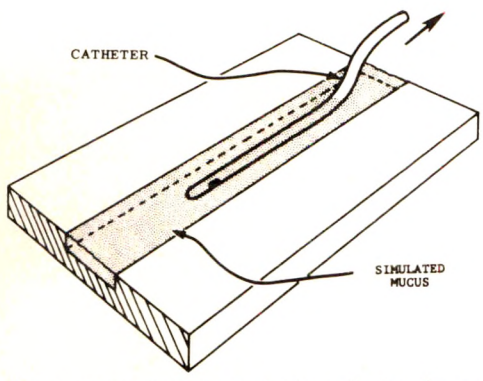


FIG 2. Tray used to evaluate catheter tip suction efficiency.

appropriate apparatus was designed for testing the suctioning efficiency of a catheter by positioning the catheter tip parallel to a simulated airway wall in contact with a thin film of mucus.

Troughs, either 2 or 3 mm deep, in flat trays (fig 2), were filled with lubricating gel of known viscosity (550 or 1200 poise) and suction was applied for 15 seconds, as the catheter tip was drawn through the film at a slow, uniform speed.

The Tri-Flo, Dual Side-Hole, and Whistle-Tip catheters were orientation sensitive. For example, the Whistle-Tip catheter suctioned essentially no gel when oriented such that the side eye did not contact the film, but aspirated a considerable amount of gel in the remaining orientations. Since during clinical suctioning the orientation of the side eye(s) of a catheter with respect to the airway wall is unknown and uncontrolled, it is necessary in determining the suction efficiency to average the amount of gel suctioned by an individual catheter over all possible orientations. Consequently, in the tray suctioning procedure, the orientation of the catheter tip was varied about a plane of symmetry in 45° increments from 0° (corresponding to "thumb-up" position of air vent) counterclockwise through 180°.

The amount of gel suctioned by the catheter in each 15-second trial was determined by weighing the catheter before and after the procedure. The catheter was cleaned between each trial and 10 trials were performed with each catheter in each orientation. For each given catheter, the numerical average of the amount of gel suctioned in all orientations has been termed the "orientation-averaged suction efficiency."

Clinical Tests.—An attempt was made to measure the suctioning efficiency of 2 catheters (Tri-Flo and Aero-Flo) in standardized suctioning procedures on patients in an intensive care unit. Four patients were suctioned in separate trials at ½-hour intervals over a 2 to 4-hour period. Two catheters were used at each suctioning procedure, with the first catheter being passed once in two of the trials and passed twice in the remaining 2 trials. The second catheter was passed additional times (usually twice) until the trachea was judged to be clear.

The first catheter used at each aspiration was alternated between the Tri-Flo and Aero-Flo, while the second catheter was not alternated. Hence, the tracheobronchial tree would be cleaned of mucus to approximately the same extent at each procedure. The mucus aspirated by each catheter was retained in an in-line mucus trap and, following each suctioning procedure, the catheters and the mucus traps were individually weighed. Consequently, the amount of mucus aspirated during single and double passes of the first catheter, as well as the remainder of the mucus removed by the second catheter, was determined for each tracheobronchial aspiration.

RESULTS AND DISCUSSION

Tracheobronchial Damage

Invagination of Mucosa.—Although it was difficult to determine with quantitative precision the transition point (in vacuum level) for each catheter between grabbing and not grabbing mucosa, several qualitative observations were made. The tendency for tissue invagination to occur was a strong function of catheter tip location and vacuum level, as well as tip design. Tissue grab always occurred, regardless of catheter type or vacuum level, when the catheter tip was "wedged" into a subsegmental bronchus of approximately the same diameter as the catheter itself, illustrating the value of withdrawing the catheter slightly before applying suction.

With the catheter tip located in lobar and segmental bronchi (with airway diameter less than 1.5 times larger than the catheter) tissue grab was observed with all catheters at both normal (100 to 300 torr) and high (>300 torr) vacuum levels. With the catheter tip in this location, the tendency to invaginate mucosa was intermittent and strongly dependent on bronchial anatomy and catheter orientation. The frequency of grabbing appeared to be lower with the multiple side-hole tip designs than with the

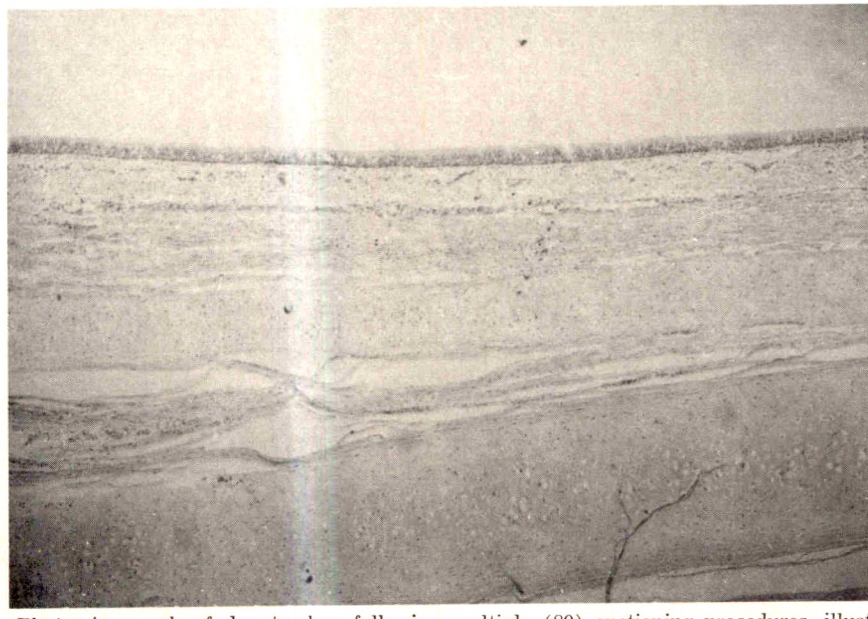


FIG 3. Photomicrograph of dog trachea following multiple (80) suctioning procedures, illustrating no loss of epithelium (H & E x 40).

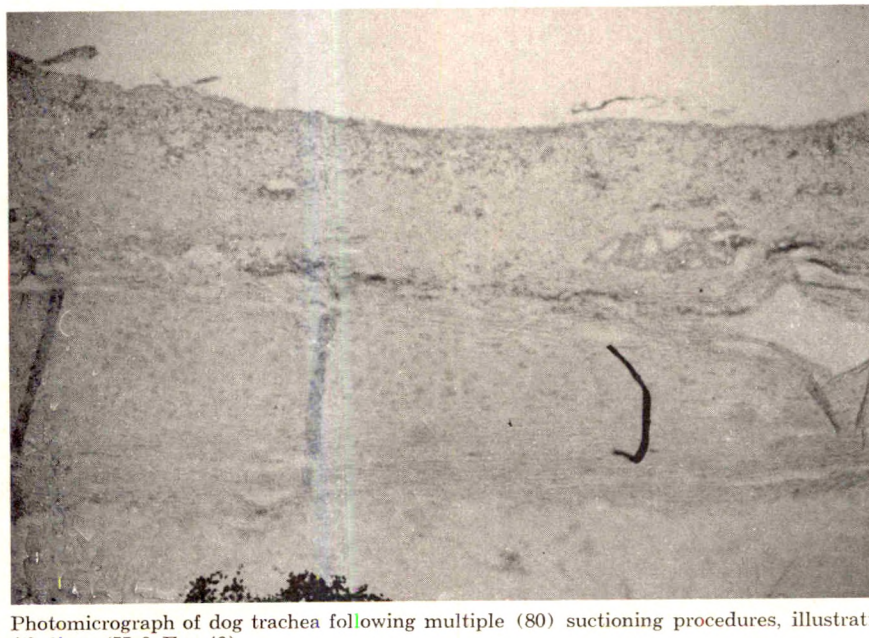


FIG 4. Photomicrograph of dog trachea following multiple (80) suctioning procedures, illustrating severe loss of epithelium (H & E x 40).

whistle-tip design, with this difference becoming more distinct as the vacuum level increased. No difference in the frequency of tissue grabbing could be distinguished between the various multiple side-hole tip designs, regardless of vacuum level. With the tip located in the trachea, mucosal grabbing was rarely observed even at high vacuum levels.

Tracheobronchial Trauma. — The results of the animal trauma studies indicate that all the catheters tested induce some degree of damage to the tracheobronchial tree. Gross observations of the airways following lung excision revealed mucosal linings which ranged in condition from being completely clear and clean to displaying multiple large, distinct hemorrhagic lesions (fig 3 and 4).

Furthermore, the degree of grossly observable damage to the tracheobronchial tree induced by any given catheter was quite variable, often spanning this entire range. Animals in which catheters were passed without applying vacuum (table 1, group 6) all displayed slight to moderate damage, with a limited number of distinct lesions. The airways in control animals, however, in which no catheters were passed (table 1, groups 7 and 8) grossly appeared quite normal, with no distinct lesions being observed.

All specimens were examined microscopically twice (on separate occasions) by a pathologist without knowing the identity of the slides. Observations recorded related to the degree of vascularity, extent of vascular dilation, epithelial loss, and presence of inflammation. Review of the histologic data revealed that the control animals in which no catheters were passed displayed various degrees of altered vascularity and inflammation similar to noncontrol animals. However, the existence of epithelial loss in the control animals in which no catheters were passed was markedly reduced compared to the noncontrol animals. Based on these observations, the presence or absence of epithelial loss was used as the histologic criterion for damage to the tracheobronchial mucosa from the suctioning procedure.

Damage Index.—To permit the direct comparison of the results of these various test groups, a numerical system of grading the degree of damage was established and a tracheobronchial *Damage Index* was defined, based on both gross and histologic observations:

0: Tracheobronchial mucosal lining was completely clear and clean under gross examination and displayed no microscopically observable loss of epithelium.

1: Minimal, questionable alterations were observed, either grossly or microscopically, which might be related to catheter suctioning.

2: Slight damage observed anywhere in the airway lining (gross and/or microscopic).

3: Moderate damage observed anywhere in the airway lining (gross and/or microscopic).

4: Severe damage observed anywhere in the airway lining (gross and/or microscopic).

Gross and microscopic observations previously tabulated were reviewed (without knowing to which animal the data corresponded) and a Damage Index was established for each animal. The range and average Damage Index for animals in each group are listed in table 2.

TABLE 2
Range and Average Tracheobronchial Damage Index in Experimental Animals Following Multiple Suctioning Procedures

Group	Catheter	Number of animals	Damage index	
			Range	Average
1	Tri-Flo	9	0-4	1.9
2	Aero-Flo	5	0-4	2.0
3	Gentle-Flo	5	1-3	2.2
4	Dual Side-Hole	4	1-3	2.0
5	Whistle-Tip	8	2-4	2.9
	Control animals			
6	Catheter*	4	2-3	2.25
7	Bronchoscope†	2	0-1	0.5
8	Clean‡	5	0-1	0.2

*One animal each with Tri-Flo, Aero-Flo, Dual Side-Hole and Whistle-Tip.
†Bronchofiberscope passed twice, no catheters passed.
‡Nothing passed into tracheobronchial tree.

The control group of dogs in which no catheters were passed (table 3, group 8) had an average Damage Index of 0.2. However, the average Damage Index of dogs suctioned with catheters containing multiple side-holes (table 1, groups 1 to 4) was significantly higher ($p<0.05$, single-tailed Student t test) ranging from 1.9 to 2.2. Considering the variability of the damage seen in the individual animals and the small number of animals in each group, the differences between the Damage Indexes of the various low-trauma catheter tip designs are not significant ($p>0.1$). On the other hand, the animals suctioned with the Whistle-Tip catheter (group 5) had an average Damage Index of 2.9, no animal having a value less than 2. This Damage Index is significantly higher than for the animals suctioned with multiple side-hole catheters ($p<0.1$).

Animals in group 6, in which catheters were passed without vacuum being applied, had an average Damage Index of 2.25. Hence, the physical act of inserting the catheter induces a measurable amount of trauma to the airway wall. Since the Damage Index of groups 1 to 4 is not significantly different from that of group 6, the damage related

TABLE 3

Amount of Aspirate Removed by Aero-Flo and Tri-Flo Catheters, as Well as Percentage of Total Aspirate Removed, in Single-Pass and Double-Pass Clinical Trials in 4 Patients

Patient	Number of samples	First catheter			Second catheter*		Portion of total aspirate removed by first catheter (average), %
		Type	Number of passes	Average aspirate, gm	Type	Average aspirate, gm	
1	3	Tri-Flo	1	1.47	Tri-Flo	3.9	28
	2	Aero-Flo	1	2.0	Tri-Flo	5.15	28
2	2	Tri-Flo	1	1.2	Tri-Flo	2.6	32
	3	Aero-Flo	1	1.9	Tri-Flo	3.5	36
3	5	Tri-Flo	2	0.67	Tri-Flo	0.33	69
	5	Aero-Flo	2	0.75	Tri-Flo	0.37	71
4	5	Tri-Flo	2	0.81	Tri-Flo	0.43	76
	5	Aero-Flo	2	0.90	Tri-Flo	0.448	69

*Second catheter was usually passed twice or until trachea was judged to be clear of mucus.

to suctioning with multiple side-holed catheters appears attributable to physically inserting the catheters and not to suctioning or mucosal grabbing. On the other hand, with the Whistle-Tip catheter, additional damage beyond that related to the insertion of the catheter seems apparent.

CATHETER SUCTION EFFICIENCY

Animal Studies.—The studies in which a given amount of simulated mucus (lubricating gel of viscosity equal to 550 poise) was injected at known locations in the trachea of dogs were unrevealing. Extreme variability in the data, even between repetitive experiments within the same animal, led to large uncertainties and low reproducibility. This was presumably due to lack of control over the location of the mucus sample and the probability of contact of the catheter tip with the mucus.

Catheter-Tip Suction Efficiency.—Since it is obviously the tip of the catheter that aspirates mucus in a suctioning procedure, the suction efficiency of the catheter tip should be indicative of its clinical suctioning effectiveness. By aspirating simulated mucus in uniform thin films in a flat trough, the randomness in the contact between the catheter tip and mucus is diminished greatly as compared to the animal studies described above. Lubricating gels of viscosities equal to 550 and 1200 poise were aspirated in thin films of 2 and 3 mm depth. (It should be noted here that, though the viscosity of the simulated mucus fell in the physiologic range,[5] the viscoelastic and non-Newtonian nature of mucus was not closely simulated.)

A significant difference in the orientation-averaged tip suctioning efficiency was exhibited between the various catheters (fig 5 and 6). For example, in a 3 mm film of lubricating gel with a viscosity of 550 poise, the suctioning efficiency of the Tri-Flo and Whistle-Tip catheters was approximately 4 times greater than the suctioning efficiency of the Aero-Flo catheter ($p<0.01$). The trend displayed by these data remained consistent as the film thickness and lubricating gel viscosity were varied.

To further simulate actual conditions during tracheobronchial suctioning, additional

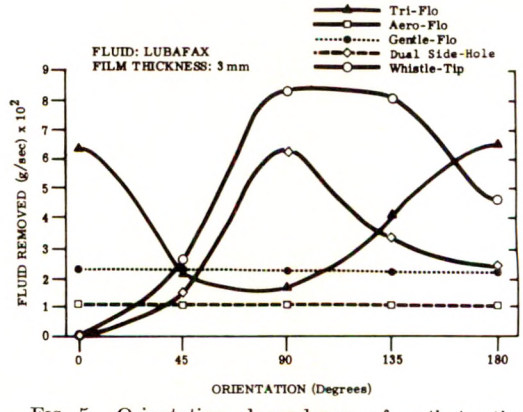


FIG 5. Orientation dependency of catheter-tip suction effectiveness in 3 mm film of lubricating mucus (viscosity = 550 poise).

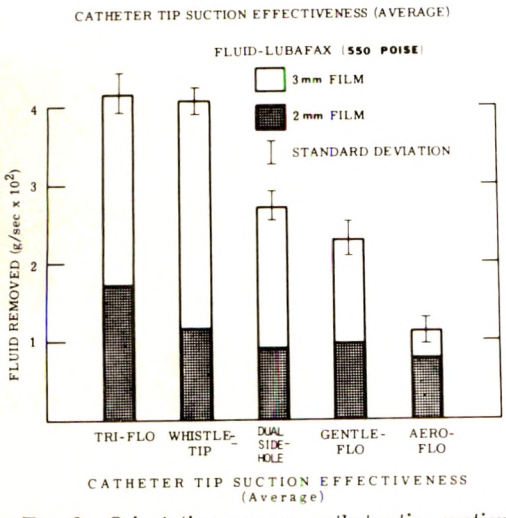


FIG 6. Orientation-average catheter-tip suction effectiveness evaluated in 2 and 3 mm films of lubricating gel (viscosity = 550 poise).

experiments were conducted with the trough inside a 2.5-cm diameter cylindrical chamber evacuated during suctioning to a pressure of -2.5 cm H_2O (corresponding to tracheal pressures measured *in vivo* during suctioning). This experiment, simulating tracheal air-flow conditions, showed no significant changes in relative uptake rates.

Clinical Trials.—In an attempt to demonstrate the influence of this measured variation in catheter-tip suction efficiency in a clinical suctioning procedure, preliminary clinical experiments were conducted in which patients were suctioned with a combination of the Tri-Flo and Aero-Flo catheters, as described previously. These two catheters were selected since they represent the highest and lowest catheter-tip suction efficiency. Each suction procedure consisted of a single or double passage of either the Tri-Flo or the Aero-Flo catheter, followed by additional passes with the Tri-Flo catheter until the tracheobronchial tree was judged to be clean. Approximately one-third of the mucus was removed during the first pass and a second third was removed during the second pass, indicating a need for multiple-pass suctioning procedures to obtain effective cleaning (table 3). No significant difference was observed in the percentage of mucus removed by either catheter in these preliminary experiments. Due to the limited number of trials and the difficulty encountered in obtaining precise data during these tests, no overall conclusions have been drawn from these data.

REFERENCES

1. Plum F, Dunning MF: Techniques for minimizing trauma to the tracheobronchial tree after tracheotomy. N Engl J Med 254:193-200, 1956

2. Shumacker HB Jr, Hampton LJ: Sudden death occurring immediately after operation in patients with cardiac disease, with particular reference to the role of aspiration through the endotracheal tube and extubation. J Thorac Surg 21:48-56, 1951

3. Rosen M, Hillard EK: The use of suction in clinical medicine. Br J Anaesth 32:486-504, 1960

4. Sackner MA, Landa JF, Greeneltch N, et al: Pathogenesis and prevention of tracheobronchial damage with suction procedures. Chest 64:284-290, 1973

5. Denton R: The rheology of human lung mucus. Ann NY Acad Sci 106:746-754, 1963

AGE AND METHOXYFLURANE NEPHROTOXICITY The influence of age on development of mechoxyflurane (MOF) nephrotoxicity was determined in Fischer 344 rats. Serum ionic fluoride after 2 hours exposure to 0.5% MOF was least in young rats (6 weeks) and highest in the 12 month old animals. Polyuria occurred only in animals more than 6 weeks old. This relative protection against MOF nephrotoxicity in young rats is probably related to less drug storage and thus less metabolite formation plus greater fluoride bone storage in these young animals. *(Bell LE, Hitt BA, Mazze RI: The influence of age on the distribution, metabolism and excretion of methoxyflurane in Fischer 344 rats: A possible relationship to nephrotoxicity. J Pharm Exp Ther 195:34-40, 1975)*

Case History Number 89:
A Life-Threatening Complication of Cricothyroid Membrane Puncture

Y. K. POON, MB, BS, FFARCS*

THIS report describes an episode of acute upper-airway obstruction secondary to extensive subcutaneous emphysema in a patient in whom a catheter was inserted through the cricothyroid membrane to aid tracheal intubation.

A 20-year-old, 142 cm, 37.2 kg man with long-standing severe rheumatoid arthritis was admitted for left total hip replacement, following a similar procedure on the right a month earlier. In addition to his short stature and multiple large joint deformities, relevant physical findings included cervical spine rigidity and limitation of movement without deformity, a small receding mandible, and large prominent upper central teeth. There was no evidence of temporomandibular or cricoarytenoid joint abnormality.

At the time of the first procedure, nasotracheal intubation was moderately difficult during N_2O-O_2-halothane anesthesia with spontaneous respiration. It was impossible to visualize the larynx, but a 6-mm tracheal tube was inserted blindly. The remainder of the anesthetic procedure was uneventful. A fiberoptic laryngoscope was not available at the time of this or the later operation.

For the second procedure, anesthesia was induced in a similar fashion, but blind nasotracheal intubation was unsuccessful after several attempts. It was then elected to thread a small catheter up through the larynx as a guide for the endotracheal tube. The cricothyroid membrane was punctured with a 17-gauge needle-over-catheter IV unit and the catheter was threaded up into the mouth. As a 7-mm orotracheal tube passed over the catheter would not enter the trachea, the catheter was directed up through the nose and a 6-mm nasotracheal tube passed over the catheter into the trachea. The catheter was removed, the tracheal tube cuff inflated, and anesthesia and operation proceeded uneventfully. Respiration was spontaneous during N_2O-O_2-halothane anesthesia. There was no evidence of subcutaneous emphysema at the termination of the surgical procedure.

The patient was extubated in the recovery room following return of consciousness. The initial postoperative course was uneventful, and the patient was transferred to his ward 90 minutes after operation. At that time, a small amount of subcutaneous air was noted in the anterior neck.

On the ward, narcotic analgesics were administered when the patient was noted to be grunting and complaining of pain at the operative site. He also complained of nasal congestion and blew his nose repeatedly. Four hours postoperatively, the subcutaneous emphysema had increased dramatically and involved the face, neck, and upper thorax, but the patient was not in respiratory distress. Forty minutes later, the subcutaneous emphysema had further progressed, with involvement of the lower trunk and increased swelling of the neck and face. The patient was now cyanotic and in obvious

*Assistant Professor, Department of Anesthesia, Health Sciences Centre-General, University of Manitoba, Winnipeg, Manitoba, Canada.

This feature is conducted by Douglas B. Craig, MD, FRCP(C), Contributing Editor, Department of Anesthesia, University of Manitoba, Winnipeg, Manitoba, Canada.

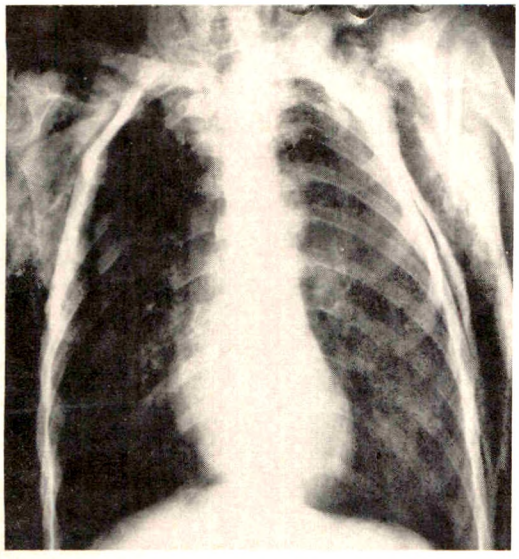


FIGURE. Supine chest (portable) radiograph, 5 hours postoperation, demonstrates extensive subcutaneous emphysema, pneumomediastinum, and right pneumothorax.

respiratory distress, with marked inspiratory stridor. A chest radiograph was taken at this time (figure).

Because of this acute deterioration, and in view of the earlier difficulties with tracheal intubation, the patient was immediately returned to the operating room for chest-tube insertion and tracheostomy. O_2 (100%) was administered by face mask and local anesthetic was infiltrated in the neck. With the skin incision, air was released from the neck with a hissing sound, immediately improving the inspiratory stridor. Exposure of the anterior trachea revealed a small puncture.

The dramatic improvement in the patient's condition made it unnecessary to proceed with the tracheostomy. A subcutaneous drain was inserted in the neck incision and was connected to suction. Arterial blood gases sampled immediately after this procedure and throughout the subsequent recovery period were normal. The right chest tube was removed after 3 days. A small left pneumothorax developed but did not require drainage. The lungs were fully expanded by the 12th postoperative day and all subcutaneous emphysema had resolved by the 18th day. The patient was discharged from hospital with no sequelae from this complication.

Discussion

DONALD H. REIMER, MD, FRCP(C)
Lecturer
Department of Anesthesia
Health Sciences Centre-General
University of Manitoba
Winnipeg, Manitoba, Canada

Puncture of the cricothyroid membrane allows rapid and relatively easy access to the lumen of the trachea, bypassing the

Comment

DOUGLAS B. CRAIG, MD, FRCP(C)

Enthusiasm for the use of technics requiring cricothyroid membrane puncture has not been accompanied by similarly increased awareness of the potential complications inherent in the procedure. This case report should serve as a dramatic reminder that major complications do occur. Air extravasation into subcutaneous tissues and the mediastinum has been the most common major complication previously reported. In this patient, the extent of the tissue emphysema, and the severity of its effects, producing airway obstruction, likely resulted from 2 factors: the generalized tissue abnormality associated with chronic severe rheumatoid arthritis, and the increased tracheal pressure due to nose blowing, promoting leakage and spread of air.

Cricothyroid membrane puncture as an aid to intubation should now rarely be required, due to the availability of reliable fiberoptic laryngoscopes. For many other situations, however, cricothyroid puncture remains part of valuable, and at times life-saving, technics. Like any other procedure, its safe use requires knowledge of its indications and contraindications, as well as the early recognition and management of complications.

mouth, pharynx, and larynx. Use of this technic has increased, associated with the introduction of venturi devices for mechanical ventilation during laryngoscopy[1] and laryngectomy.[2] The percutaneous transtracheal ventilation technic has been the subject of a recent review.[3] Other procedures utilizing cricothyroid membrane puncture have included tracheal lavage and sputum sampling,[4] local anesthetic spraying of the trachea,[5] bronchography,[6] emergency ventilation,[7] and guiding of endotracheal tubes over catheters inserted upward into the pharynx.[8]

Although the tissues pierced are thin, it is possible for air, blood, bacteria, contrast media, and needle debris to enter the soft tissues of the neck, where they may produce serious complications. As illustrated by this case report, any postpuncture increase in tracheal pressure, such as that produced by exhalation against a closed glottis as in grunting or coughing, or by high-pressure gas insufflation, increases the risk of air leakage into subcutaneous tissue. Larger-bore needles and catheters increase the likelihood of air leakage. It has been suggested that the incidence and severity of tissue emphysema can be minimized by inserting the needle through the skin at some distance from the tracheal perforation site and by application of pressure to the anterior neck after removal of the catheter.[9]

Subcutaneous emphysema localized to the neck occurred in 5/102 patients and 2/13 volunteers reported by Kalinske and associates.[4] Two in each group developed mediastinal emphysema. A case of severe, life-threatening mediastinal emphysema, reported by Massey,[10] resembles the course of events in our patient. In both cases, air leakage appears to have been the result of high intratracheal pressures produced by the patient in the postpuncture period. The nose-blowing by our patient would likely produce intratracheal pressures considerably higher than would grunting, and therefore explains the severity of his course. Another contributing factor was likely a generalized tissue abnormality associated with his chronic illness and debility.

Respiratory infections increase the hazard of mediastinal infection, and bleeding diatheses increase the risk of hematoma formation. Hemoptysis following cricothyroid membrane puncture is frequent, moderate, and usually transient.[4] One case of hypoxic death thought to be due to blood obstructing the trachea has been reported.[11] Wound infections are now rare. Two patients with tuberculous granulomas of the needle tract in the neck were reported by Pecora.[12] Breakage of needles has occurred when patients have suddenly coughed with the needle in place.[13] Bradycardia, cardiac arrest, and arrhythmias have occurred in unpremedicated patients and where tracheal suction produced hypoxemia in critically ill patients.[11] Vomiting and aspiration have been reported, as well as one incident of respiratory arrest, likely caused by pain and vagal stimulation.[11]

The most common minor complaints are neck pain or sore throat, occurring in 50% of patients following transtracheal bronchography.[6] Transient hoarseness and dysphonia are also common.

This report serves as a reminder that serious complications following cricothyroid membrane puncture can and do occur. Their incidence and severity should be minimized if the following guidelines are followed:

1. Awareness of the potential complications due to air extravasation associated with increased airway pressure. This may occur during ventilation using positive pressure or when airway pressure increases with grunting, coughing, sneezing, or nose-blowing.

2. Avoiding the procedure in patients with bleeding diatheses and those with severe cough. Severe connective tissue diseases should be considered a relative contraindication.

3. Applying pressure to the puncture wound for several minutes and keeping the patient flat in bed for several hours.

4. Using the smallest-bore needle and catheter possible.

5. Administering supplemental O_2 if the patient is already hypoxemic or if suctioning is to be performed.

6. Recognizing complications early and treating them appropriately.

REFERENCES

1. Spoerel WE, Greenway RE: Technique of ventilation during endolaryngeal surgery under general anaesthesia. Can Anaesth Soc J 20:369-377, 1973

2. Carden E, Crutchfield W: Anaesthesia for microsurgery of the larynx. Can Anaesth Soc J 20: 378-389, 1973

3. Smith RB, Schaer WB, Pfaeffle H: Percutaneous transtracheal ventilation for anaesthesia and resuscitation: a review and report of complications. Can Anaesth Soc J 22:607-612, 1975

4. Kalinske RW, Parker RH, Brandt D, et al: Diagnostic usefulness and safety of transtracheal aspiration. N Engl J Med 276:604-608, 1967

5. Bonica JJ: Transtracheal anesthesia for endotracheal intubation. Anesthesiology 10:736-738, 1949

6. Reams GB, Bosnick MA: Bronchography through puncture of the cricothyroid membrane. J Thorac Cardiovasc Surg 40:117-124, 1960

7. Jacob HG: Emergency percutaneous transtracheal catheter and ventilator. J Trauma 12:50-55, 1972

8. Powell WF, Ozdil T: A translaryngeal guide for tracheal intubation. Anesth & Analg 46:231-234, 1967

9. Smith RB: Transtracheal ventilation during anesthesia. Anesth & Analg 53:225-228, 1974

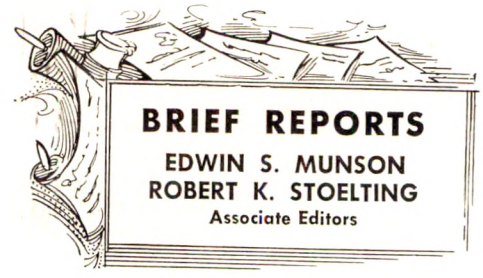
10. Massey JY: Complications of transtracheal aspiration. J Arkansas Med Soc 67:254-256, 1971

11. Spencer CD, Beatty HN: Complications of transtracheal aspiration. N Engl J Med 286:304-306, 1972

12. Pecora DV: Comparison of transtracheal aspiration with other methods of determining bacterial flora of the lower respiratory tract. N Engl J Med 269:664-666, 1963

13. Adriani J, Parmley J: Complications following transtracheal anesthesia. Am J Surg 84:11-12, 1952

PEEP, PCWP and CARDIAC OUTPUT The authors investigated the effect of PEEP upon the pulmonary circulation in 12 patients requiring postoperative mechanical ventilation. Cardiac index did not change with 5 or 10 cm H_2O PEEP but decreased at levels above 10 cm H_2O. The fall in cardiac output was frequently accompanied by a marked increase in PCWP. The authors speculate that high intra-aveolar pressures created by PEEP restrict flow through the pulmonary circulation and decrease cardiac output. Furthermore, in this situation, a balloon-tipped catheter no longer reflects left atrial pressure but rather the higher alveolar pressure which has occluded the pulmonary capillaries. It would be incorrect to consider the increase in PCWP as evidence of volume overload or left ventricular failure. During PEEP, a high PCWP may reflect high resistance to flow in the pulmonary circulation and a need to reduce the level of PEEP to permit maintenance of an adequate cardiac output. *(Hobelman CF, Smith DE, Virgilio RW et al: Hemodynamic alterations with positive end-expiratory pressure: The contribution of the pulmonary vasculature. J Trauma 15:951-958, 1975)*



An Unusual Problem in Nasotracheal Extubation

GARRY S. SKLAR, MD*
ANTONIO E. ALFONSO, MD†
BENTON D. KING, MD‡
Brooklyn, New York§

NASOTRACHEAL intubation is widely used for prolonged intubation and for certain operations around the mouth. We wish to report an unusual problem in extubation and to recommend precautionary measures.

REPORT OF A CASE

A 69-year-old man underwent partial glossectomy with N_2O-O_2-droperidol-fentanyl anesthesia with an 8.5 mm nasotracheal tube. The cuff and inflation tube were added to the endotracheal tube and a plastic adapter was added to the syringe end of the inflation tube. The inflation tube was not fused to the main tube.

After an uneventful anesthetic procedure and recovery, as the nasotracheal tube was withdrawn from the trachea, larynx, pharynx, and nose, the inflation tube and adapter were pulled, as if around a pulley, into the patient's nose (fig 1). The entire endotracheal tube was out of the patient's nose, but traction on the inflation tube was un-

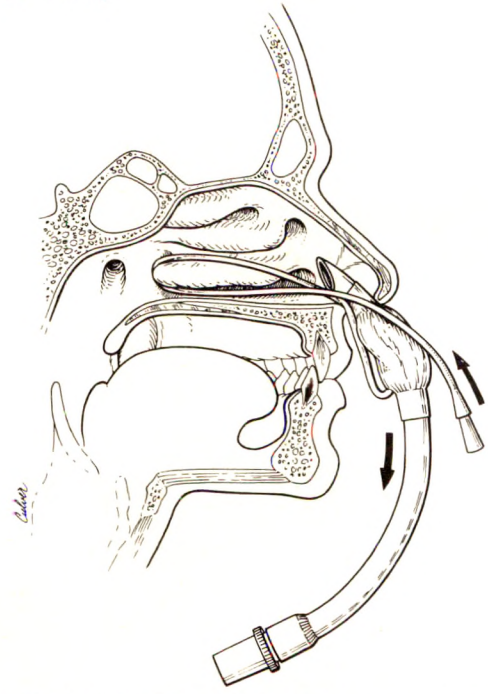


FIG 1. Inflation tube being drawn into nostril by "pulley" action of turbinate.

*Instructor, Department of Anesthesiology.
†Assistant Professor, Department of Surgery.
‡Professor and Chairman, Department of Anesthesiology.
§Departments of Anesthesiology and Surgery, State University Hospital, State University of New York, Downstate Medical Center College of Medicine, Brooklyn, New York 11203.

Paper received: 7/23/75
Accepted for publication: 8/4/75

FIG 2. How plastic adapter probably caused inflation tube to be trapped in nostril.

successful in dislodging the trapped end, because of the plastic adapter (fig 2).

The problem was solved by cutting the inflation tube, sewing the end of it to a nasogastric tube, passing the nasogastric tube into the same nostril, and retrieving it through the mouth with the attached inflation tube and plastic adapter following.

COMMENT

The inflation tube had undoubtedly become wrapped around a nasal turbinate. Forceful pulling could only result in unnecessary trauma and would only wedge the plastic adapter against the turbinate. The nasogastric tube allowed the adapter to change direction and thus be removed through the mouth.

In retrospect, as the inflation tube was pulled into the nostril during extraction of the endotracheal tube, the plastic adapter should have been removed; this probably would have allowed the inflation tube to be removed without difficulty. Had the plastic adapter come off in the nose, the potential danger of infection or aspiration would arise.

This incident suggests the desirability of using endotracheal tubes with integral cuffs and fused inflation tubes, or inflation tubes with a soft tapered rubber end for inflation, for nasotracheal intubation. It should also be noted that the fused joint of inflation tubes on reusable endotracheal tubes with integral cuffs may become separated with repeated use and sterilization. Thus, frequently used tubes should be employed with caution.

A recent review[1] of complications of tracheal intubation did not mention this problem, nor is it mentioned in standard anesthesia texts. Awareness of this unusual occurrence and its management should help prevent future mishaps of this nature.

REFERENCE

1. Blanc VF, Tremblay NAG: The complications of tracheal intubation: a new classification with a review of the literature. Anesth & Analg 53:202-213, 1974

A Simple Method of Inserting a Nasogastric Tube for Anesthesia

ANIS BARAKA, MD*

MANY different technics for the insertion of a nasogastric tube have been recommended.[1-10] A simple technic, originally proposed by Conroy,[2] is to introduce the nasogastric tube via an endotracheal tube inserted through the nose into the esophagus.

An alternative method is to introduce the nasogastric tube via a rectal tube, which also can be inserted blindly through the nose into the esophagus and even into the stomach. The firm but flexible wall of the rectal tube, its adequate length, and its smooth terminal outlet make it more suitable than an endotracheal tube for blind nasoesophageal intubation (figure).

*Chairman, Department of Anesthesiology, American University of Beirut, Beirut, Lebanon.

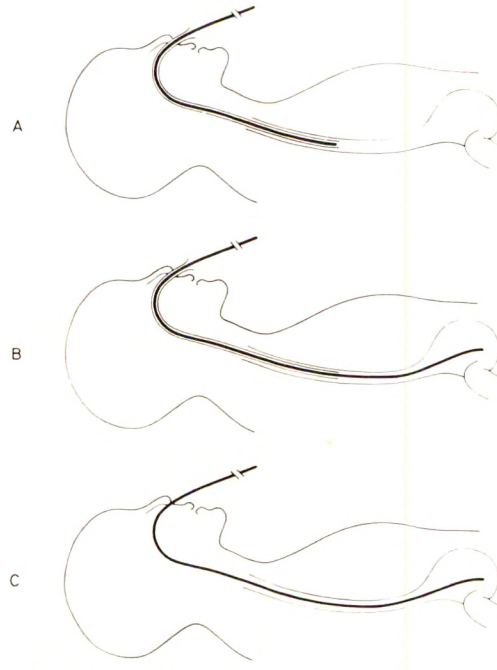


FIGURE. Technic of inserting nasogastric and rectal tubes: A. Rectal tube, enclosing nasogastric tube, is inserted blindly from nose into esophagus. B. Nasogastric tube is then threaded further through rectal tube into stomach. C. Rectal tube is withdrawn while nasogastric tube is left in place.

REFERENCES

1. Lundy JS: Clinical Anesthesia. Philadelphia, WB Saunders Company, 1942, p 386

2. Conroy WA: Insertion of gastric tubes in the unconscious patient. Anesthesiology 4:81, 1943

3. Steen TR: A method of passing Ryle's tubes in anaesthetized patients. Br J Anaesth 23:234, 1951

4. Cohen DD, Fox RM: Nasogastric intubation in the anesthetized patient. Anesth & Analg 42: 578-580, 1963

5. Ogawa H: A reliable technique for insertion of a gastric tube during operation. Surg Gynecol Obstet 132:497, 1971

6. Tahir AH, Adriani J: A method of inserting a nasogastric tube in the anesthetized or comatose patient. Anesth & Analg 50: 179-180, 1971

7. Matsuki A, Zsigmond EK: Simple and reliable method of inserting a nasogastric tube during anaesthesia. Br J Anaesth 44:610, 1972

8. Wedley JR: Simple and reliable method of inserting a nasogastric tube during anaesthesia. Br J Anaesth 44:1117, 1972

9. Virtue RW: Simple and reliable method of inserting a nasogastric tube during anaesthesia. Br J Anaesth 45:234, 1973

10. Mirakhur RK: Simple and reliable method of inserting a nasogastric tube during anaesthesia. Br J Anaesth 45:1062, 1973

Acute Cardiovascular Collapse After Intravenous Phytonadione

PAUL BARASH, MD*
LUKE M. KITAHATA, MD, PhD†
SAMUEL MANDEL, MD‡
New Haven, Connecticut§

ALTHOUGH a clinical impression[1,2] exists that phytonadione (AquaMephyton®) given IV can in rare cases cause hypotension, review of the literature reveals no documentation of this impression. The following case report suggests that phytonadione given IV may, however, be associated with cardiovascular collapse.

REPORT OF A CASE

A 43-year-old man with squamous cell carcinoma of the vocal cord entered Yale-New Haven Hospital for a total laryngectomy. He had been admitted 10 months before for evaluation and treatment of Laennec's cirrhosis. During the prior admission, carcinoma of the left vocal cord was also

*Assistant Professor of Anesthesiology.
†Professor and Chairman of Anesthesiology.
‡Assistant Professor of Anesthesiology.
§Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut 06510.

Paper received: 6/27/75
Accepted for publication: 7/15/75

diagnosed, for which the patient received radiotherapy. A liver biopsy at that time revealed severe nutritional cirrhosis and alcoholic hepatitis. The patient gave a history of heavy alcoholic ingestion over a number of years; he was also a heavy cigarette smoker (3 packs/day). His only previous operation was uneventful removal of a "cyst on the spine" 20 years previously.

At the time of the present admission, the patient had hoarseness and occasional bilirubinuria, but otherwise was free of symptoms. His weight was 64 kg, and his vital signs were normal. Pertinent positive physical findings revealed the stigmata of liver disease: palmar erythema, gynecomastia, hepatosplenomegaly, and ascites.

Laboratory data showed hemoglobin of 10.8% and a platelet count of 160,000/ml. Urinalysis was negative. Prothrombin time was 14.2 sec (control 10.8 sec) and partial thromboplastin time 43 sec (control 31.5 sec). Serum electrolytes (mEq/L) were Na^+ 134, Cl^- 85, K^+ 3.1, and HCO_3 38. Total protein was 7 gm % (albumin 2.5 gm % and globulin 4.5 gm %). Liver profile showed total serum bilirubin to be 2.22 mg % (direct 1.86%), SGOT 60 μ (normal <35 μ), ammonia 176 mg %, cephalin flocculation 4+, and thymol turbidity 8.4 μ (normal <5 μ); serum amylase, lipase, LDH, and alkaline phosphatase were all normal. Chest x-ray revealed a left pleural effusion. ECG showed sinus tachycardia and T-wave abnormality "suggestive of electrolyte abnormality or drug effect."

At 0630 hr, the patient was premedicated with diazepam (10 mg) and scopolamine (0.5 mg) IM. Prior to induction at 0830, an intra-arterial line and a thermodilution Swan-Ganz catheter[3] were placed. Induction of anesthesia was with 20 mg of IV diazepam. Orotracheal intubation was facilitated with 10 mg of IV pancuronium. Anesthesia was then maintained with O_2-halothane (99:1). A tracheostomy was performed and the airway was then secured with a right-angle spiral-wire endotracheal tube (Boyan) through the tracheal stoma. Operation proceeded uneventfully.

Vital signs remained stable throughout the next 5 hours of operation, with blood pressure 150/90 torr, pulmonary artery pressure (PAP) 25/14 torr (table), pulse rate 100, and adequate hourly urine output. Albumin, whole blood, and lactated Ringer's solution were used for volume replacement.

At 1300 hr, halothane was discontinued and the patient received O_2 while the dressing was applied. At 1315, since there was still persistent oozing from the cutaneous suture line, 10 mg of phytonadione was injected IV over 10 minutes. Five minutes later, there was a precipitous drop in BP to 30/10 torr and a drop in PAP to 10/5 torr. The ECG showed a sinus rhythm at a rate of 80/minute. The patient immediately was placed in Trendelenburg position and $CaCl_2$ (1 gm), mephentermine (30 mg), dexamethasone (8 mg) were given IV. In addition, lactated Ringer's solution, whole blood, and fresh frozen plasma were administered. Within 3 minutes, the BP rose to 80/50 torr and returned to the prehypotensive level within 10 minutes.

Upon arrival in the recovery room, the patient was responsive to his name and could move all extremities. However, 45 minutes later, increased bleeding necessitated reexploration of the surgical incision, under general anesthesia, which revealed several bleeding points. These were suture ligated.

At 1900 hr, because of prolonged prothrombin time, an additional dose of 25 mg of phytonadione was administered IM, without incident. On the 2nd postoperative day, 10 mg of phytonadione was administered IV in 100 ml of D/5-0.2 N saline solution over 1 hour, without untoward effect. The remainder of his hospital course was uneventful.

DISCUSSION

Phytonadione is the aqueous colloidal solution of vitamin K_1. Parenteral administration is indicated where the oral route is contraindicated or in emergency situations. According to Udall,[4] phytonadione should be administered IV in emergency situations where a severe coagulation defect is present secondary to a decreased amount of vitamin K_1. Absorption from an IM injection in this situation can be erratic and should not be relied upon. However, because the action of vitamin K_1 is detectable only 3 hours after IV administration, fresh frozen plasma should be given during this latent period, if bleeding secondary to hypoprothrombinemia is severe.

The etiology of the hypotension in the present case is conjectural. With the acute decrease in PAP, it would appear that the hypotension was caused by peripheral vasodilation and accompanied by a fall in PAP

TABLE
Significant Cardiorespiratory Measurements

Time	BP, torr	PAP, torr	pH	$Paco_2$, torr	Pao_2, torr	$P\bar{v}o_2$	BE/ mEq/L	Fio_2	Hct	Cardiac output, L/min
Preop	130/80		7.50	38	69		+5	0.21	30	
1015 hr	150/100	28/17	7.63	30	426	56	+11	0.99	30	7.76
1100 hr	150/100	25/16	7.60	29	375	58	+10	0.99	32	6.37
1230 hr	150/90	25/14	7.57	32	441	64	+8	0.99	29	5.90
1330 hr	30/10	10/5								
1345 hr	150/90	25/9	7.59	23	110		+5	1.0	36	5.70
1410 hr	150/90	25/9	7.54	30	351		+4	1.0	37	

rather than a rise, which would have been expected if myocardial depression were a major cause. This acute decrease in PAP suggests that left ventricular failure was not present, but it does not necessarily rule out the presence of right ventricular failure. However, the latter is unlikely, since the cardiac output of 5.7 L/min was obtained only 15 minutes later (table). Therefore, a primary myocardial etiology of the hypotension is unlikely, so it appears that peripheral vasodilation was primarily responsible.

The patient was stable, no medications were administered, and no surgical manipulation was performed during this period. Further, the anesthetic procedure had been terminated 25 minutes before the onset of hypotension. Therefore, it is highly unlikely that there was a temporal relationship to any event other than the administration of vitamin K_1.

An allergic or anaphylactic response is doubtful, since the patient had subsequent injections (an IM injection 6 hours postoperatively and a prolonged IV injection over a 1-hour period on the 2nd postoperative day) without untoward effects. Thus, it appears that either the emulsion (polyethylated fatty-acid derivatives and dextrose) or the active drug has a peripheral vasodilating effect.[5]

The present case is the first documented report of a vascular reaction to IV phytonadione, although fatal reactions have been reported with other types of fat emulsions.[2] There have been no reports of fatalities associated with parenteral use of water-soluble vitamin K analogues, but these are ineffective in treating drug-induced hypoprothrombinemia.[2] The fact that the hypotension followed IV administration of phytonadione could be explained on the basis of higher blood levels associated with IV injection.

The placement of a Swan-Ganz catheter in this case was fortuitous in documenting the precipitous drop in PAP associated with a drop in systemic arterial pressure following IV injection of phytonadione.

This case suggests that therapy for hypotension following injection of phytonadione should be directed at correcting the acute peripheral vasodilation.

REFERENCES

1. Today's Drugs: Vitamin K. Br Med J 2:40, 1969

2. Uses and hazards of vitamin K drugs. Med Lett 5:98-99, 1963

3. Forrester JS, Ganz W, Diamond G, et al: Thermodilution cardiac output determination with single flow directed catheter. Am Heart J 83:306-311, 1972

4. Udall JA: Don't use the wrong vitamin K. Calif Med 112:65-67, 1970

5. Cohn VA: Fat soluble vitamins III, vitamin K and vitamin E, The Pharmacologic Basis of Therapeutics. Edited by LS Goodman, A Gilman. New York, The Macmillan Company, 1970, pp 1690-1694

IN THE NEXT ISSUE

Scientific Articles

May-June 1976

ANESTHETIC CONSIDERATIONS FOR PERICARDECTOMY IN UREMIC PERICARDIAL EFFUSION—Halappa N. Konchigeri, M.D., and Sidney Levitsky, M.D., Chicago, Illinois.

AN EVALUATION OF MEMORY UNDER REGIONAL ANESTHESIA WITH IV LORAZEPAM AS A PREMEDICANT—Harry A. Taub, Ph.D., and Louis Eisenberg, M.D., Syracuse, New York.

CLINICAL INVESTIGATION OF A NEW INTRAVENOUS ANESTHETIC—ETOXADROL HYDROCHLORIDE (CL-1848C; U-37862A)—E. L. Frederickson, M.D., David E. Longnecker, M.D., and Gary W. Allen, M.D., Atlanta, Georgia, Charlottesville, Virginia and Temple, Texas.

OUTPATIENT EVALUATION: A NEW ROLE FOR THE ANESTHESIOLOGIST—Elizabeth A. M. Frost, M.D., Bronx, New York.

FACTORS AFFECTING A-aDO_2 AFTER OPEN HEART SURGERY — Atsuo Sari, M.D., Yoshiaki Okuda, M.D., Hiroshi Takeshita, M.D., and Tatsuroh Oda, M.D., Ube Yamaguchi, Japan.

THOUGHTS ABOUT MEDICAL WRITING. XXXV—Charles G. Roland, M.D., Rochester, Minnesota.

CIRCULATORY RESPONSES AND HALOTHANE CONCENTRATIONS DURING GASTRIC OR GALLBLADDER TRACTION WITH AND WITHOUT NEUROMUSCULAR BLOCKADE—Robert K. Stoelting, M.D., Christine Peterson, R.N., and James A. Madura, M.D., Indianapolis, Indiana.

ARTERIAL HYPOXEMIA CAUSED BY INTRAVENOUS KETAMINE—Elémer K. Zsigmond, M.D., A. Matuski, M.D., S. P. Kothary, M.B.B.S., and M. Jallad, B.S., Ann Arbor Michigan, and Aomori-Ken, Japan.

ANALYSIS OF TASKS AND HUMAN FACTORS IN ANESTHESIA FOR CORONARY-ARTERY BYPASS—Peter J. Kennedy, M.S., Alfred Feingold, M.D., Earl L. Wiener, Ph.D., and Ronald S. Hosek, Ph.D., Miami, Florida.

THE EFFECT OF ENFLURANE, ISOFLURANE, FLUROXENE, METHOXYFLURANE, AND DIETHYL ETHER ANESTHESIA ON OUABAIN TOLERANCE IN THE DOG—Anthony I. Ivankovich, M.D., David J. Miletich, Ph.D., Ronald K. Grossman, M.D., Ronald F. Albrecht, M.D., Adel A. El-Etr, M.D., and Vincent J. Cairoli, Ph.D., Chicago, and Maywood, Illinois.

METHOXYFLURANE BIOTRANSFORMATION AND RENAL FUNCTION FOLLOWING METHOXYFLURANE ADMINISTRATION FOR VAGINAL DELIVERY OR CESAREAN SECTION—Steven R. Young, M.D., Robert K. Stoelting, M.D., Virginia K. Bond, M.D., and Christine Peterson, R.N., Indianapolis, Indiana.

BUTORPHANOL AND MORPHINE: A DOUBLE-BLIND COMPARISON OF THEIR PARENTERAL ANALGESIC ACTIVITY—M. Tavakoli, M.D., G. Corssen, M.D., and F. S. Caruso, Ph.D., Birmingham, Alabama, and Syracuse, New York.

AN UNUSUAL COMPLICATION OF LUMBOSACRAL PLEXUS BLOCK: A CASE REPORT—Stanley Muravchick, Ph.D., M.D., and William D. Owens, M.D., St. Louis, Missouri.

PEDIATRIC NITROUS OXIDE ENCEPHALOGRAPHY: 5 YEAR EXPERIENCE WITH 457 CASES—Richard A. Elwyn, M.D., Wallace H. Ring, M.D., and Edward Loesser, M.D., Salt Lake City, Utah.

THE LATERAL SITTING POSITION FOR NEUROSURGERY—Francisco Garcia-Bengochea, M.D., Edwin S. Munson, M.D., and James V. Freeman, M.D., Gainesville, Florida.

ISOPROTERENOL AND PROPRANOLOL DO NOT ALTER MAC IN DOGS—Yasumasa Tanifuji, M.D., and Edmond I. Eger, II, M.D., San Francisco, California.

HEPATIC CLEARANCE OF LIDOCAINE IN THE PRESENCE OF ANESTHETIC AGENTS—Robert G. Burney, M.D., and Cosmo A. DiFazio, Ph.D., M.D., Charlottesville, Virginia.

ENDOBRONCHIAL ANESTHESIA FOR NON-INTRATHORACIC SURGERY—Jay B. Brodsky, M.D., Michael D. Abramowitz, M.D., and Mary P. Mehrez, M.D., Boston, Massachusetts.

PROLONGED NEUROMUSCULAR BLOCKADE ASSOCIATED WITH TRIMETHAPHAN—Susan L. Wilson, M.D., Robert N. Miller, M.D., Carmen Wright, C.R.N.A., and Diane Hasse, C.R.N.A., St. Louis, Missouri.

UNRELENTING HYPOTENSION ASSOCIATED WITH AN ACUTE ABDOMEN IN A COMATOSE HEMOPHILIAC—Robert W. Vaughan, M.D., Susan Wilson, M.D., Lawrence S. Waldbaum, M.D., St. Louis, Missouri.

PERFORMANCE OF IMMERSION HEATER HUMIDIFIERS. I. INSPIRED AIR TEMPERATURE—K. P. Geevarghese, M.D., J. Antonio Aldrete, M.D., and T. C. Patel, M.D., Louisville, Kentucky, and Denver, Colorado.

LARYNGOTRACHEAL SECRETIONS DURING ENDOTRACHEAL ANESTHESIA—Chong M. Lee, M.D., and James E. Gildea, M.D., Hershey, Pennsylvania.

THE EFFECT OF GENERAL ANESTHETIC AGENTS, OUABAIN AND ALDOSTERONE, ON STRIATED MUSCLE CONTRACTION IN TOAD—L. Amaranth, M.D., and Nikaan B. Andersen, M.D., Cleveland, Ohio.

CASE HISTORY #90—CARDIAC DECOMPENSATION ASSOCIATED WITH MYOTONIA DYSTROPHICA DURING ENFLURANE ANESTHESIA—Paul G. Barash, M.D., and Michael Meyers, M.D., New Haven, Connecticut.

BRIEF REPORTS

HYPERCAPNIA DURING CYCLOPROPANE ANESTHESIA—Stephen T. Barasch, M.D., Sandra Booth, C.R.N.A., and Jerome H. Modell, M.D., Gainesville, Florida.

DEFECTIVE DISPOSABLE ENDOTRACHEAL TUBE—Tai-Mao Chiu, M.D., and Elsie F. Meyers, M.D., St. Louis, Missouri.

FATAL COMPLICATIONS FOLLOWING LONG-TERM INTUBATION: A CASE REPORT—Gunnar A. Kroesen, M.D., and Bruno C. Haid, M.D., Innsbruck, Austria.

CALIBRATION OF THE NARKOTEST® GAS MONITOR FOR ISOFLURANE—Jose L. Velazquez, M.D., and Alfred Feingold, M.S., M.D., Miami, Florida.

A Guide for Authors

Anesthesia and Analgesia . . . Current Researches invites original manuscripts on subjects pertinent to the specialty of anesthesiology. Original articles accepted for publication, or papers presented at the Society's annual scientific meetings which subsequently may be published in the Journal, become the property of the International Anesthesia Research Society. Reproduction in whole or in part is not permitted except by written consent of the publisher and the author.

Submit manuscripts in triplicate to—
T. H. Seldon, M.D., Editor
Kahler East, Suite C
Rochester, Minnesota 55901, U.S.A.

All papers are reviewed by the Editorial Board and other selected referees. If accepted for publication, editorial revisions may be made to aid clarity and understanding without altering the meaning. Edited copy is submitted to authors for approval before it is sent to the printer. Page proof will be submitted to authors for final approval. Reprint order forms will accompany page proof.

Titles should be concise but informative, with thought given to the use of key words for indexing. Ninety characters, including punctuation and spaces, should be sufficient.

Coauthors' names should be followed by the major degree, professional affiliation, and address.

Abstract: On the first page of manuscript, an abstract of from 50 to 250 words, according to length of article, but not exceeding one double-spaced typed page, should describe purpose, methods, results, and conclusions, as succinctly as possible. This replaces both former Capsule Review and Summary, but is the same in content and format.

Type manuscript (in triplicate) on 8½ x 11-inch white paper, with 1½ inch margins at top, bottom, and both sides. Double space ALL typing, including references, legends and footnotes.

References: About 20 references are acceptable. In extensive reviews of the literature, readers will be advised that longer reference citations can be obtained from author. Citations should include (1) last name of author followed by initials without internal punctuation; (2) commas separate names and initials of authors; (3) four or more authors are designated as "et al;" (4) journal name is abbreviated according to Index Medicus style; (5) references from books show (a) city of publication, name of publisher, date of publication, after book title; (6) journal references give volume, first and last page numbers, year. (See previous issues of *Anesth & Analg* for style.)

Tables should be self-explanatory and should supplement, not duplicate, the text.

Photographs should have sharp contrast, be on *glossy* paper unmounted, and 4 by 5 inches or larger. *Polaroid prints damage easily in handling and thus may reproduce indistinctly. Glossy prints are preferred.* Submit photographs of roentgenograms with contrasts as in original and sharply defined; "TOP" must be identified. All illustrative materials, charts, etc., must be submitted in triplicate, clearly numbered according to text and legend.

Lettering on charts and graphs must be large enough to be legible when reduced in size. Curves, scatter dots, etc., should contrast with reference lines.

Drawings must be in black (India) ink on white background and should be of professional quality.

Legends for illustrations should be concise and typed on one page. Legends for photomicrographs should show stain and magnification data.

Drug names used in the text should be generic unless trade names are essential to the discussion.

Multiple Publication: To avoid violating existing copyrights, a statement should accompany each submitted article indicating that the material in question:

1. Has not been simultaneously submitted to another journal.
2. Has not been previously published elsewhere.

a. Abstracts of 400 words or less do not constitute prior publication.

b. A report issued by requirement of a governmental agency or comparable granting institution does not constitute prior publication.

c. Extracting by news media does not constitute prior publication unless all vital tables and pertinent conclusions are involved or unless such publication was actively solicited by the authors.

Legal considerations require letters of permission from authors and publishers for use of illustrations or quotations originally appearing elsewhere, and also written permission for use of photographs of identifiable patients. Identifying information, such as names, initials, hospital numbers, and dates, must be avoided.

When experimentation involving human subjects is reported, an appropriate statement regarding informed consent should be made.

Case reports should include only significant data. Laboratory findings should be restricted to those pertinent to the discussion.

Symbols used for respiratory physiology should follow Fed. Proc. 9:602, 1950.

Explanation of abbreviations and symbols used within the text should be added as a footnote.

Example: torr: Unit of pressure of 1 mm. of mercury at 0° C. and standard gravity.

CHECK LIST

- ☐ Title
- ☐ Authors
- ☐ Abstract
- ☐ Text
- ☐ Tables
- ☐ References
- ☐ Figures
- ☐ Legends

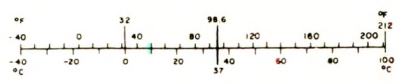
Manuscripts and all illustrations should be mailed flat, *in triplicate,* with cardboard protection. The author should retain one complete copy, including tables and illustrations.

Metric Conversions

HEIGHT			WEIGHT	
Cm	Feet	Inches (approx.)	Kilograms	Pounds
15	0 ft.	6 in.	1	2.2
30	1 ft.	0 in.	5	11
45	1 ft.	8 in.	10	22
60	1 ft.	11½ in.	15	33
75	2 ft.	5½ in.	20	44
105	3 ft.	5 in.	25	55
115	3 ft.	9 in.	30	66
120	3 ft.	11 in.	35	77
125	4 ft.	1 in.	40	88
130	4 ft.	3 in.	45	99
135	4 ft.	5 in.	50	110
140	4 ft.	7 in.	55	121
145	4 ft.	9 in.	60	132
150	4 ft.	11 in.	65	143
155	5 ft.	1 in.	70	154
160	5 ft.	3 in.	75	165
165	5 ft.	5 in.	80	176
170	5 ft.	7 in.	85	187
175	5 ft.	9 in.	90	198
180	5 ft.	11 in.	95	209
185	6 ft.	1 in.	100	220
190	6 ft.	3 in.	105	231
195	6 ft.	5 in.	110	242
200	6 ft.	7 in.	115	253
205	6 ft.	9 in.	120	264
210	6 ft.	11 in.	125	275
215	7 ft.	1 in.		

APPROXIMATE CONVERSIONS FROM METRIC MEASURES

Symbol	When You Know	Multiply by	To Find	Symbol
	LENGTH			
mm	millimeters	0.04	inches	in
cm	centimeters	0.4	inches	in
m	meters	3.3	feet	ft
m	meters	1.1	yards	yd
km	kilometers	0.6	miles	mi
Symbol	When You Know	Multiply by	To Find	Symbol
	MASS (weight)			
g	grams	0.035	ounces	oz
kg	kilograms	2.2	pounds	lb
t	tonnes (1000 kg.)	1.1	short tons	
Symbol	When You Know	Multiply by	To Find	Symbol
	TEMPERATURE (exact)			
°F	Fahrenheit temperature	5/9 (after subtracting 32)	Celsius temperature	°C



Anesthesia and Analgesia CURRENT RESEARCHES

BACK ISSUES AVAILABLE

Available at $3.00 Per Issue

Vol.	Year	Numbers Available						Vol.	Year	Numbers Available					
33	1954	–	2	3	4	5	6	41	1962	–	2	3	–	5	6
34	1955	1	2	3	4	5	6	42	1963	–	–	3	4	5	6
35	1956	1	2	3	4	5	6	43	1964	–	2	–	–	–	6
36	1957	–	–	–	–	–	6	44	1965	–	2	3	4	5	6
37	1958	1	2	3	4	5	6	45	1966	–	2	–	–	–	6
38	1959	–	2	3	4	–	6	46	1967	–	–	3	–	–	6
39	1960	–	–	3	4	5	6	47	1968	–	–	3	4	5	6
40	1961	–	–	3	4	5	6	48	1969	1	2	3	–	5	–

Available at $4.50 Per Issue

Vol.	Year	Numbers Available						Vol.	Year	Numbers Available					
49	1970	1	–	–	–	5	6	53	1974	–	2	3	4	–	6
50	1971	1	2	3	–	–	–	54	1975	1	2	–	–	–	6
51	1972	–	2	3	–	5	6	55	1976	1					
52	1973	1	2	3	4	–	–								

SINGLE ISSUES PRIOR TO 1954: Write to publisher at address below for listing of issues available at $2.00 each.

BOUND VOLUMES AVAILABLE: $8.00—For Years 1947, 1948, 1949; $10.00—For Years 1953, 1955

OTHER PUBLICATIONS AVAILABLE:

"Basic and Clinical Physiology of the Liver" (Supplement to Sept.-Oct. 1965 issue)—$3.00.

Ten-Year (1960-1969) Cumulative Index—$3.00.

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, Ohio 44122

Please send me the publications circled above, or listed hereunder:

☐ Check for $_____ enclosed.

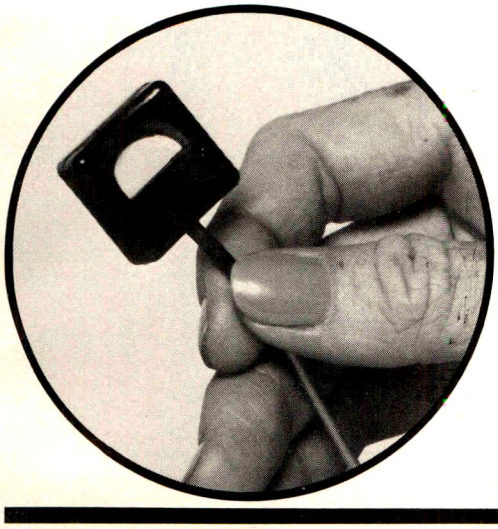
☐ Please send bill with understanding that ordered material will be sent when payment is received.

Name_____

Address_____

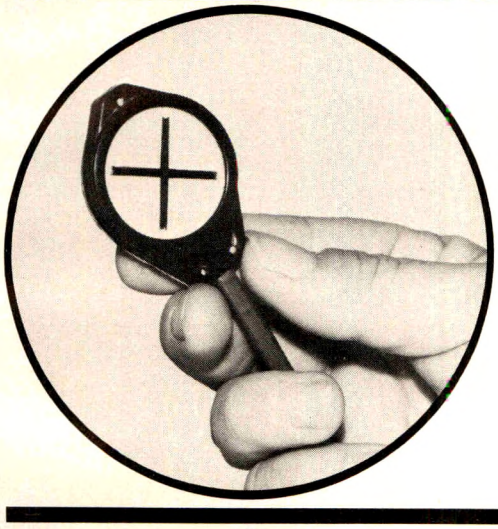
City, State, Zip_____

VERSATONE® MULTI-PURPOSE DOPPLER INSTRUMENT



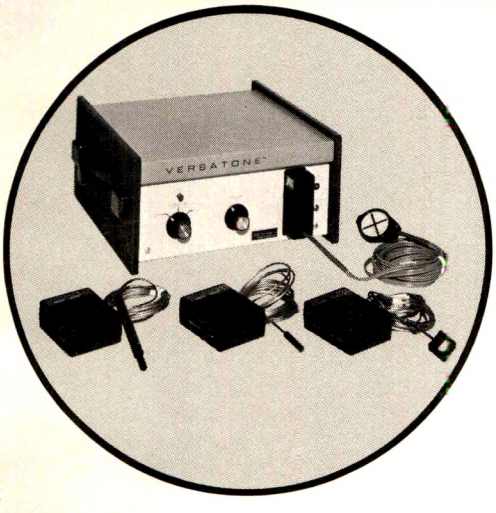
FOR MONITORING DOPPLER SOUNDS OF BLOOD FLOW AND TO TAKE DOPPLER SYSTOLIC BLOOD PRESSURE

This sensitive Doppler probe is easy to tape in position for non-invasive detection and monitoring of arterial blood flow during surgery. Used with an occlusive cuff and manometer, systolic blood pressures may be obtained even on infants and hypotensive patients.



FOR EARLY DETECTION OF VENOUS AIR EMBOLISM

This sensitive wide-angle Doppler probe is particularly well suited for the detection of venous air emboli which may occur during neurosurgical procedures performed with the patient in the upright position. It also detects motion of the heart muscle, heart valves and blood flow.



VERSATONE D8 DOPPLER

The Model D8 VERSATONE Doppler instrument is designed to use interchangeable probes of various frequencies and configurations. It is powered by a rechargeable battery and has a built-in loudspeaker. Options include an electrocautery sensor and cut-out, a molded earset for private listening, and a chart recording circuit. The two probes shown above are particularly useful to the anesthesiologist. Two sizes of pencil shaped probes are also available. These are useful for intraoperative assessment of flow in exposed vessels, as well as for transcutaneous flow detection.

MED SONICS

For more information call or write:
P.O. Box M (340 Pioneer Way) Mountain View, CA (415) 965-3333

In 16 years of use in the United States, FLUOTHANE (halothane) has been administered over 100 million times in a wide variety of surgical procedures. 100 million ...extensive usage and evaluation that attests to FLUOTHANE as the most widely used inhalant anesthetic.

Since it was first introduced, over 4,000 papers worldwide have been published, ranging from review articles to in-depth studies. 4,000 papers... a bibliographic record of note on the most widely used inhalant anesthetic.

In a continuing program of informational services on anesthesiology, Ayerst provides printed and audiovisual aids reflecting the opinions and experiences of recognized authorities in the field. These include the highly regarded series on *Anesthesia Rounds* and *Clinical Aspects of Anesthesiology*, as well as several films of educational value—all available through your Ayerst Representative.

FLUOTHANE® (HALOTHANE) ...OVER 100 MILLION ADMINISTRATIONS

- nonflammable, nonexplosive
- permits use of high concentrations of oxygen
- allows free use of cautery for more adequate control of bleeding
- minimal odor facilitates smooth, rapid induction, reduces patient distress
- early obtundation of pharyngeal and laryngeal reflexes facilitates intubation
- lessens airway problems
- permits rapid adjustment of depth of anesthesia
- emergence is rapid and tranquil with quick recovery of protective reflexes
- minimal nausea and vomiting, shorter recovery room stay

Ayerst®

See last page of advertisement for prescribing information.

FLUOTHANE®

brand of halothane

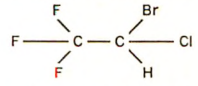
the most widely used inhalant anesthetic

from **Ayerst**

for precision, experience, quality, and service

(Complete text of package circular.)

Description. FLUOTHANE, brand of halothane, is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20° C., and the boiling point (range) is 49° C.-51° C. at 760 mm. Hg. The vapor pressure is 243 mm. Hg at 20° C. The blood/gas coefficient is 2.5 at 37° C., and the olive oil/water coefficient is 220 at 37° C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. FLUOTHANE is soluble in rubber, some plastics, and similar materials; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizing bottles not specifically designed for its use. It is recommended that vaporizers be emptied at the end of each operating day. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE should be avoided when a previous exposure was followed by fever and jaundice, or when there was an unexplained postoperative fever.

FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy: Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

Adverse Reactions. The following adverse reactions have been reported: hepatic necrosis, cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

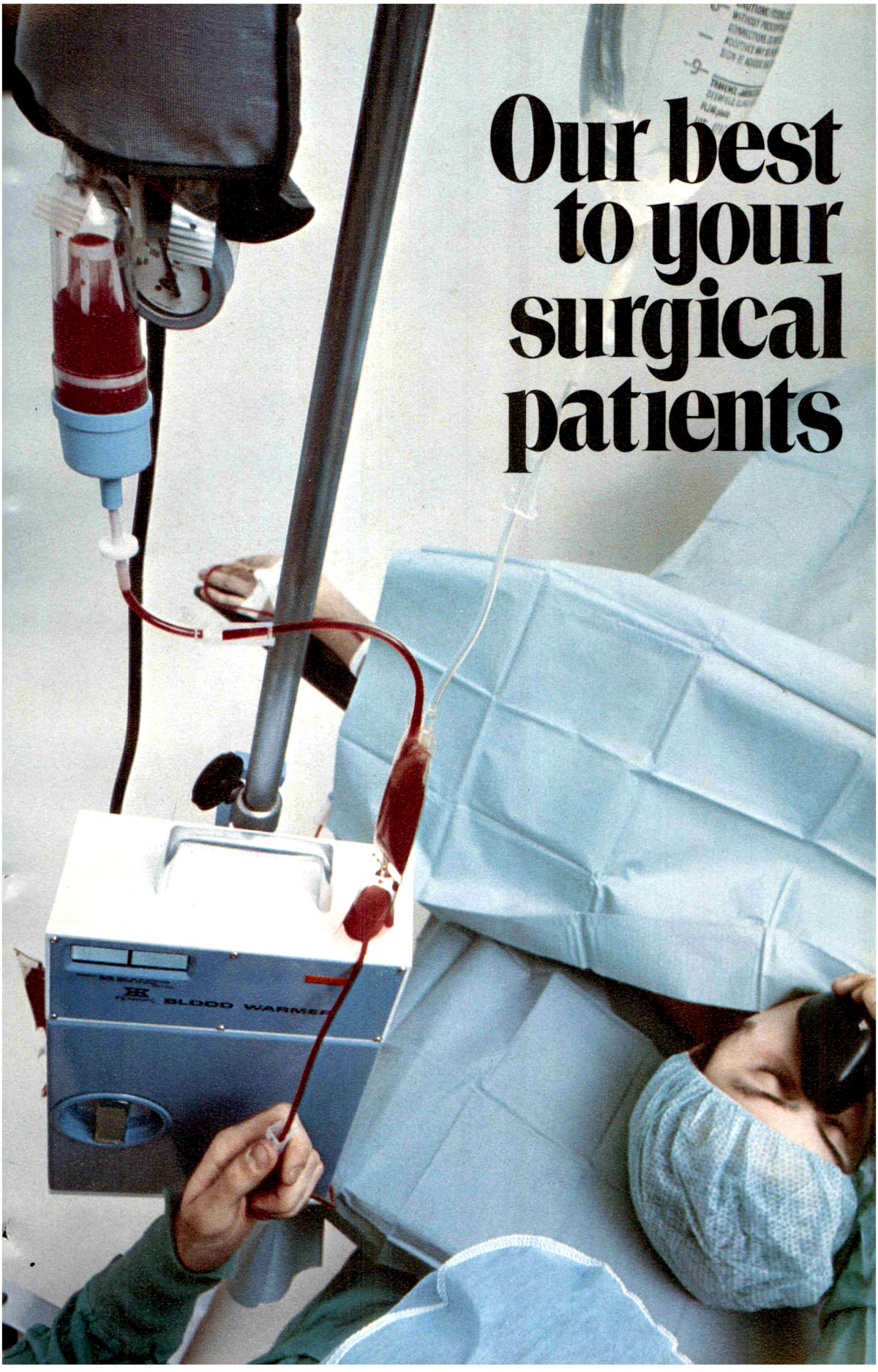
Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide (usually in a 50:50 ratio).

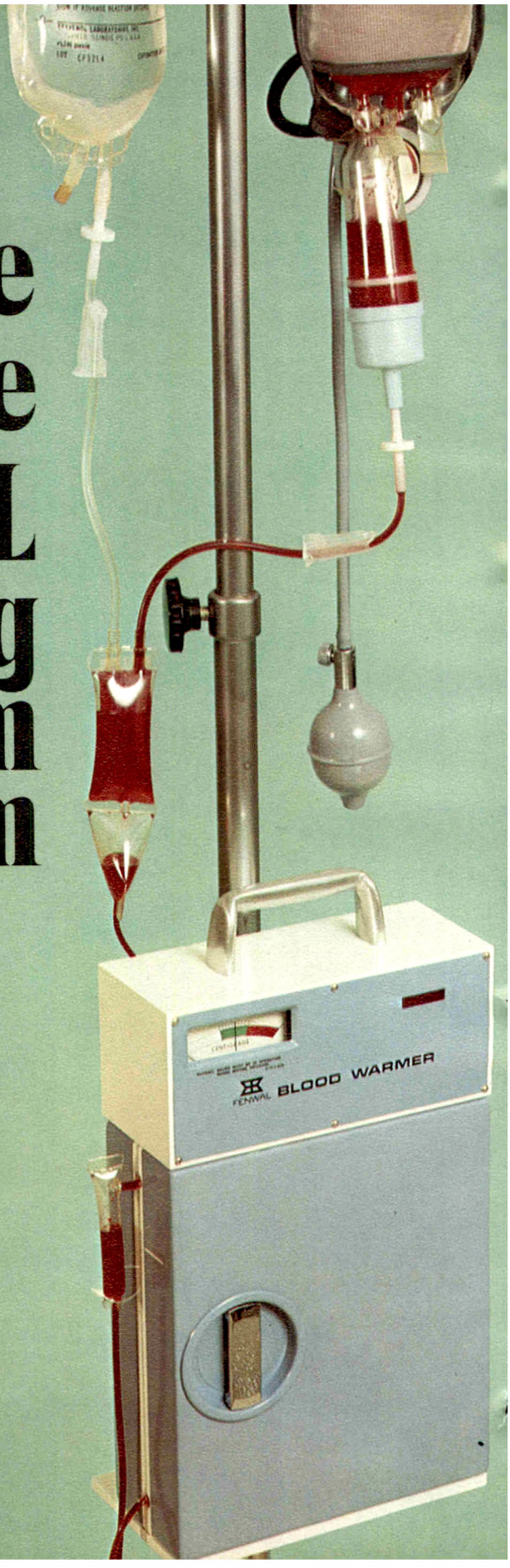
How Supplied. No. 3125—Unit packages of 125 cc. and 250 cc. of halothane stabilized with 0.01% thymol (w/w).

7522

Ayerst AYERST LABORATORIES
New York, N.Y. 10017


Our best
to your
surgical
patients

The complete FENWAL operating room system



The Fenwal Dry Heat Blood Warmer is designed for use during single or multiple transfusions when precise regulation of blood temperature and flow rate is indicated. It utilizes a disposable plastic blood-warming pathway.

Fenwal Recipient Sets are available to accommodate your infusion requirements. The Single Lead Set is to be used for the intravenous administration of one unit of whole blood, red cells or plasma. The "Y" Recipient Set is designed to permit dual hookups for simultaneous administration of blood and/or solutions. The Triple Lead Set may be employed in multiple infusion procedures, i.e., blood, solutions, blood components and medication.

The Fenwal Microaggregate Blood Filter is designed to remove microaggregates down to 20 microns in size during intravenous administration of stored whole blood or red cells.

Fenwal Pressure Infusors provide an efficient non-air-dependent method for the rapid infusion of whole blood or red cells.

The Fenwal TYPENEX™ Blood Recipient Identification System ties together the identity of the transfusion candidate, his cross-match request form, blood sample and up to 10 cross-matched units of blood.

The Fenwal Venous Pressure Manometer Set is a disposable, preassembled unit that permits continuous monitoring of the patient's venous pressure while performing one simple hookup.

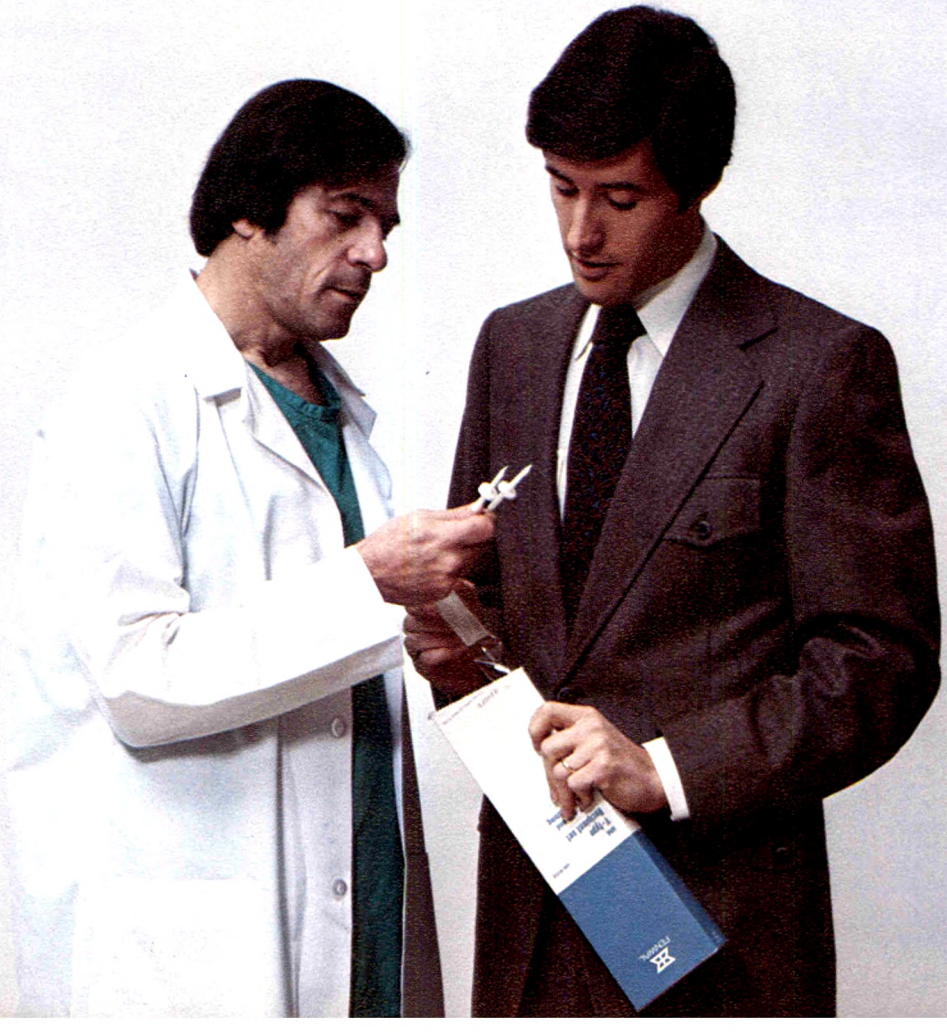
The Fenwal Platelet Recipient Set is designed specifically for the infusion of fresh blood and pool platelet concentrates.

Our best to you

Fenwal Laboratories has long been identified with innovation in modern blood handling systems. Our knowledge and experience in developing and providing sophisticated blood processing systems have earned a reputation for excellence. Thoroughly researched and tested to meet the demands of the medical profession, you can expect the same quality in Fenwal operating room devices that helped achieve our recognition with the nation's blood banks.

The Fenwal Specialist in your hospital can provide you and the other members of the operating team with completely detailed information on all of our products. Intensive training makes him fully qualified to answer your most involved questions regarding up-to-date blood transfusion procedure. Be sure to see your Fenwal Specialist the next time he visits your department.

FENWAL LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois, U.S.A. 60015.



Uncommon Endotracheal Tubes From The Most Commonly Known Name In Anesthesia

Now here's a disposable endo tube worthy of the OHIO name!

Uncuffed, or with anatomically designed cuffs for a gentle seal. Clear tubes, Murphy eye, radiopaque tips, depth markings. And a unique inflation and pilot balloon assembly.

OHIO now makes a wide range of sizes. Each tube, sterile packed, for one-patient use.

It's common knowledge that OHIO is the leader in anesthesia equipment. A dependable supplier of inhalation agents and medical gases.

Now, watch us move ahead in disposables. Endo tubes, an anesthesia breathing circuit, filters, masks, airways, suction valves, catheters, tubing . . . And more coming. With many distribution and delivery facilities to keep you supplied.

Write for Catalog # 2604. Or contact your OHIO representative about disposables. For the common good of you and your patients.

Ohio Medical Products

AIRCO®

P. O. Box 1319, Dept. A&A
3030 Airco Drive
Madison, Wisconsin 53701

The tender touch

These soft, pliable blood pressure cuffs are ideal for use on newborns and infants. Incorporating a Latex bladder, minimizing any chances for skin irritation, and Silicon wrap-around with 12-inch inflating tube. They are secured by the Velcro hook and pile method, with no eyes to hook nor ends to tuck in. They are instantly peeled apart for easy removal.

Cuffs are available in two sizes:
22080 - 1⅜ x 5" (new born)
22081 - 2¼ x 6" (infant)

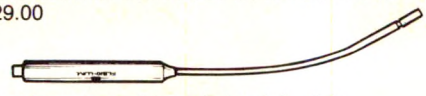
For additional information write for brochure number 27.

DUPACO
INCORPORATED
P.O. Box 98,
San Marcos, CA 92069

The new standard in patient care

Prism Laryngoscope, designed to simplify difficult intubations. Enables insertion of an endotrocheal tube with an unobstructed line of vision. Packaged sterile and complete with reusable light.

Cat. No. 9041 includes sterile prism Laryngoscope and Laryngolite, Pack/3 $15.50
Cat. No. 9040 Laryngoscope blades only, sterile, Box/10 $29.50
Cat. No. 1022 Laryngolite, designed to provide illumination for Cat. No. 9040, sterile, Box/10 $29.00



Flexi-Lum, box of three lighted, flexible intubation stylettes. High intensity, laryngoscope bulb on tip of 10" flexible shaft. Two long-lasting AA alkaline batteries with on-off backswitch. Reliable, non-flickering performance until batteries are depleted. Excellent for intubation guidelight, emergency anesthesia light or blind intubation procedures.
Cat. No. 3034, 10" flexible shaft, Pack/3 $31.02

concept INC. **We put ideas to work.**
12707 U.S. Highway 19 South
Clearwater, Florida 33516

Laryngeal mirror attachment for 006 penlight. Use for viewing posterior pharynx and larynx when anesthetizing prior to bronchoscopy. Packaged 10 per box.
Cat. No. 1506
1-11 boxes $4.25 each
12 + boxes $4.00 each

Tongue Clamp, patented self-locking ratchet with quick thumb release. Excellent for "grabbing" and holding tongue forward in either emergency or routine anesthesia use. Disposable.

Cat. No. 9000, Box/150 $15.75

Doctor's Six Pak, high-intensity, non-flickering beam, six lights per pack. Batteries not replaceable.
Cat. No. 1006
1-2 Six Paks, $7.00 each
3-5 Six Paks, $6.50 each
6 + Six Paks, $6.00 each

If not available from your dealer, order direct from Concept, Inc.

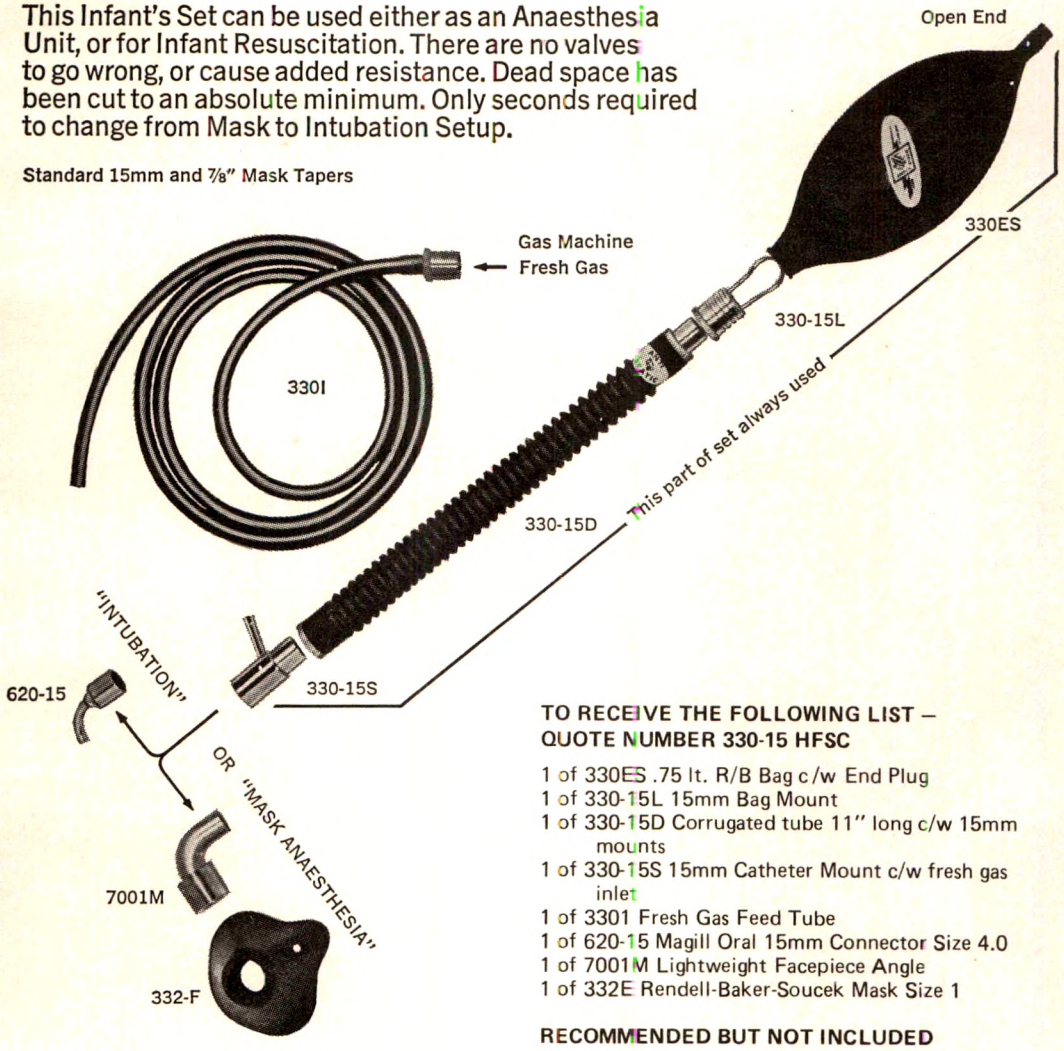
Florida residents add 4% sales tax.

JACKSON-REES MODIFICATION OF AYRE'S T-PIECE

as used by leading children's hospitals

This Infant's Set can be used either as an Anaesthesia Unit, or for Infant Resuscitation. There are no valves to go wrong, or cause added resistance. Dead space has been cut to an absolute minimum. Only seconds required to change from Mask to Intubation Setup.

Standard 15mm and 7/8" Mask Tapers



We recommend you purchase a 330LC Leather Case to store this equipment — prevents loss or damage.

TO RECEIVE THE FOLLOWING LIST — QUOTE NUMBER 330-15 HFSC

1 of 330ES .75 lt. R/B Bag c/w End Plug
1 of 330-15L 15mm Bag Mount
1 of 330-15D Corrugated tube 11" long c/w 15mm mounts
1 of 330-15S 15mm Catheter Mount c/w fresh gas inlet
1 of 3301 Fresh Gas Feed Tube
1 of 620-15 Magill Oral 15mm Connector Size 4.0
1 of 7001M Lightweight Facepiece Angle
1 of 332E Rendell-Baker-Soucek Mask Size 1

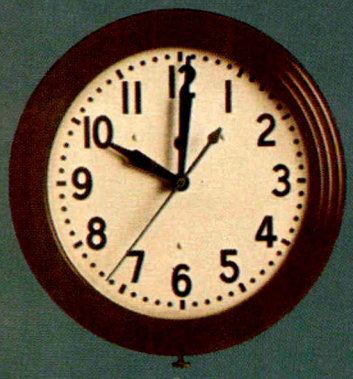
RECOMMENDED BUT NOT INCLUDED

6 (1 each) 330CF Foregger Coles Tubes 8 to 18 F.G.
1 No. 332F Rendell-Baker-Soucek Mask Size 2
1 No. 332L Rendell-Baker-Soucek Mask Size 3
1 330LC Leather Case
1 of 330-15D Corrugated tube c/w 15mm mounts.

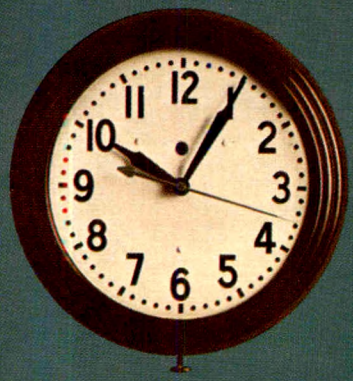
MIE

MEDICAL & INDUSTRIAL EQUIPMENT
A division of Claudius Ash Incorporated
655 - 73rd Street, Niagara Falls, New York 14304

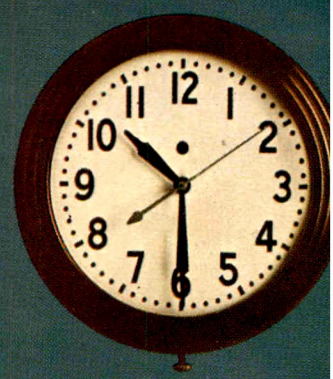
SEND FOR COMPLETE LITERATURE



SUBLIMAZE® (fentanyl) has a uniquely short duration of analgesic action—for more precise control and minimal risk of prolonged narcotic effects.

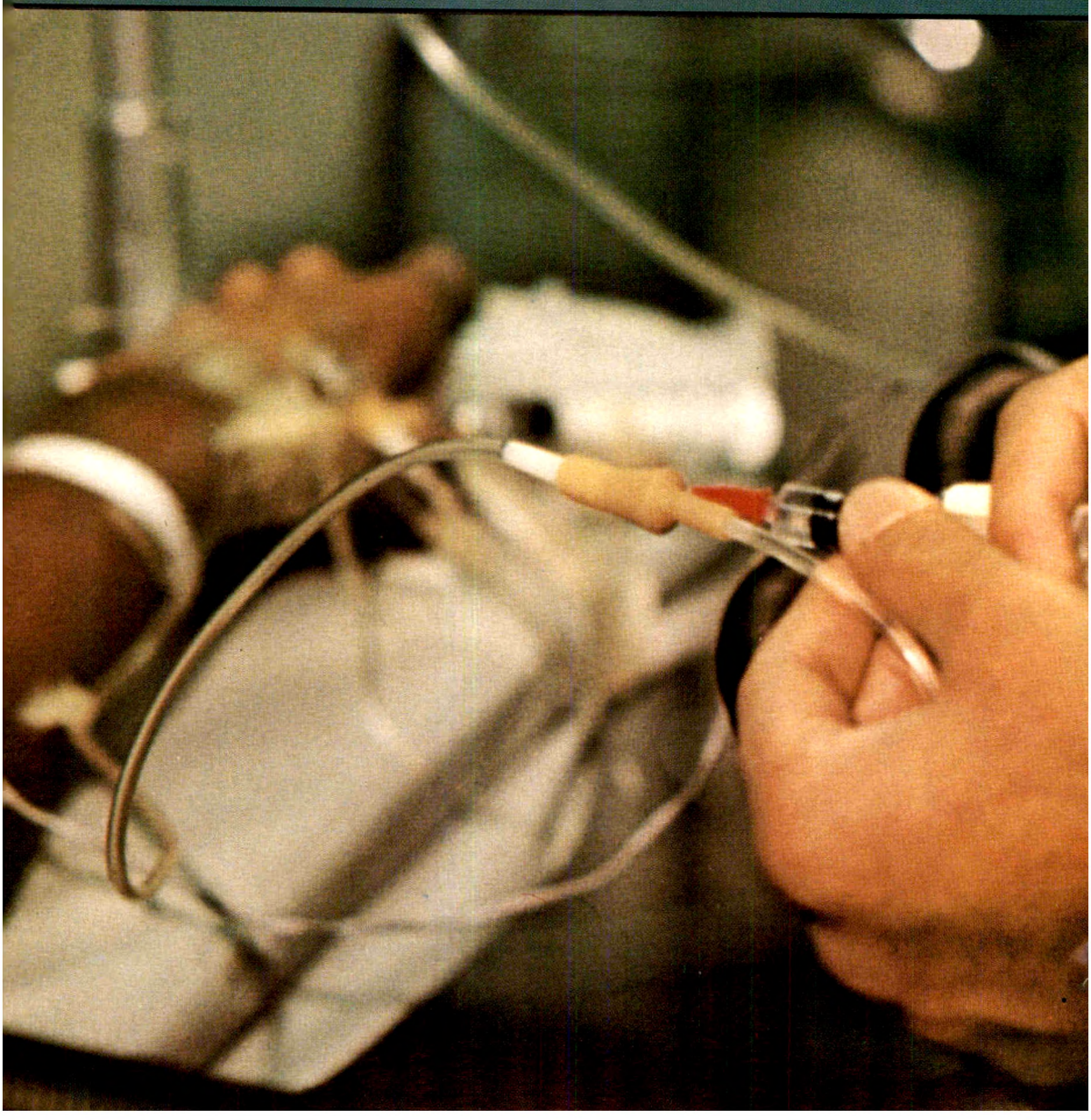


Within 5 minutes I.V., SUBLIMAZE® (fentanyl) reaches its peak analgesic effect.



Within 30 to 60 minutes I.V., the analgesic effect of SUBLIMAZE® (fentanyl) is almost completely dissipated.†

† Respiratory depressant effects may last longer than the analgesia and are increased and prolonged with large doses, multiple doses or use of postoperative narcotic analgesics.



For potent narcotic analgesic action with rapid onset and short duration:

SUBLIMAZE fentanyl provides profound analgesia without hypnosis and with little or no sedation. With this analgesia as a foundation, it is possible to use light general anesthesia in most cases.

SUBLIMAZE fentanyl is particularly suited for maintenance of analgesia after INNOVAR® injection* has been used for induction. It may also be used preoperatively, during surgery with any common general or regional anesthetic agent, and in the immediate postoperative period whenever the need for potent analgesic action arises.

SUBLIMAZE fentanyl is available both alone and as a component of INNOVAR injection.*

*INNOVAR injection is composed of a 50:1 mixture of droperidol 2.5 mg./cc. and fentanyl 0.05 mg./cc., with lactic acid for adjustment of pH to 3.5 ± 0.3.

SUBLIMAZE® (fentanyl) offers:

☐ Almost immediate analgesia—peak effect within 5 minutes I.V., 8 minutes I.M.

☐ Short duration of analgesic action—30 to 60 minutes with a single I.V. dose of up to 0.1 mg. (Respiratory depressant effects may last longer than the analgesia and are increased and prolonged with larger doses, multiple doses or use of postoperative narcotic analgesics.)

☐ No evidence of liver, heart, or kidney toxicity—expecially valuable in poor-risk patients. However, the drug should be administered cautiously in the presence of liver or kidney dysfunction or cardiac arrhythmias, and the dose should be appropriately reduced in poor-risk patients.

☐ Immediate reversibility by narcotic antagonists.

☐ Little or no histamine release—decreasing the risk of cardiovascular instability.

☐ Minimal emetic effect—has been used successfully to prepare nonfasting patients for awake intubation.

☐ Prevention or reversal of emergence delirium and tachypnea.

SUBLIMAZE® Ⓒ II (fentanyl) injection

0.05 mg./cc. as the citrate.
Warning: May be habit forming.
Sodium hydroxide for adjustment of pH to 4.0—7.5

INNOVAR® injection and SUBLIMAZE® (fentanyl) injection are available for use only upon direction of a physician. For information relating to Contraindications, Warnings, Precautions and Adverse Reactions for SUBLIMAZE fentanyl, please turn page.

© McNeil Laboratories, Inc., 1974

SUBLIMAZE® (fentanyl) injection

Description
Each cc. contains:
Fentanyl as the citrate.....0.05 mg.
Warning—May be habit forming.
Sodium hydroxide for adjustment of pH to 4.0–7.5
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY.

Actions SUBLIMAZE fentanyl is a narcotic analgesic with actions qualitatively similar to those of morphine and meperidine. SUBLIMAZE fentanyl in a dose of 0.1 mg. (2.0 cc.) is approximately equivalent in analgesic activity to 10 mg. of morphine or 75 mg. of meperidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. SUBLIMAZE fentanyl appears to have less emetic activity than other narcotic analgesics. Histamine assays and skin wheal testing in man, as well as *in vivo* testing in dogs, indicate that histamine release rarely occurs with SUBLIMAZE fentanyl.

SUBLIMAZE fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. It may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia, and bronchoconstriction.

The onset of action of SUBLIMAZE fentanyl is almost immediate when the drug is given intravenously; however, maximal analgesic and respiratory depressant effect may not be noted for several minutes. The average duration of action of the analgesic effect is 30 to 60 minutes. Following intramuscular administration, the onset of action is from seven to eight minutes, and the duration of action is from one to two hours.

Although the duration of the respiratory depressant effect is unknown, as with other narcotic analgesics it may be considerably longer than the analgesic effect.

Indications SUBLIMAZE fentanyl is indicated:
—for analgesic action of short duration during the anesthetic periods, premedication, induction, and maintenance, and in the immediate postoperative period (recovery room) as the need arises.
—for use as a narcotic analgesic supplement in general or regional anesthesia.
—for administration with a neuroleptic such as INAPSINE® (droperidol) injection as an anesthetic premedication,for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.

Contraindications SUBLIMAZE fentanyl is contraindicated in patients who are hypersensitive to the drug.

Warnings PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* FENTANYL SHOULD HAVE APPROPRIATE SURVEILLANCE.

RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

If SUBLIMAZE fentanyl is administered with a tranquilizer such as INAPSINE droperidol, the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE fentanyl persists longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as 1/4 to 1/3 those usually recommended. A neuromuscular blocking agent compatible with the patient's condition may be required to control muscle rigidity which may develop with the use of SUBLIMAZE fentanyl.

Drug Dependence: SUBLIMAZE fentanyl can produce drug dependence of the morphine type and therefore has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE fentanyl in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure: SUBLIMAZE fentanyl should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition, SUBLIMAZE fentanyl may obscure the clinical course of patients with head injury.

Usage in Children: The safety of SUBLIMAZE fentanyl in children younger than two years of age has not been established.

Usage in Pregnancy: The safe use of SUBLIMAZE fentanyl has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

Precautions *The initial dose of SUBLIMAZE fentanyl should be appropriately reduced in elderly, debilitated and other poor risk patients. The effect of the initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal a thesia and some peridural anesthetics, can alter respiratio blocking intercostal nerves. Through other mechanisms (see tions) SUBLIMAZE fentanyl can also alter respiration. W SUBLIMAZE fentanyl is used to supplement these forms of a thesia, the anesthetist should be familiar with the physiolog alterations involved, and be prepared to manage them in patients selected for these forms of anesthesia. When used wi tranquilizer such as INAPSINE droperidol, blood pressure ma altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE fentanyl should be used with caution in patie with chronic obstructive pulmonary disease, patients with creased respiratory reserve, and others with potentially comp mised respiration. In such patients, narcotics may addition decrease respiratory drive and increase airway resistance. Dur anesthesia, this can be managed by assisted or controlled resp tion. Postoperatively, respiratory depression caused by narc analgesics can be reversed by narcotic antagonists (levallorph nalorphine, and naloxone; consult individual prescribing infor tion before using). Should respiration be compromised by mus rigidity, assisted or controlled respiration and possibly a neu muscular blocking agent will be required. The occurrence muscle rigidity is related to the speed of intravenous injection a the incidence can be reduced by slow intravenous injection.

When a tranquilizer such as INAPSINE droperidol is used w SUBLIMAZE fentanyl, pulmonary arterial pressure may be creased. This fact should be considered by those who cond diagnostic and surgical procedures where interpretation of p monary arterial pressure measurements might determine fi management of the patient.

Other CNS depressant drugs (e.g. barbiturates, tranquilize narcotics, and general anesthetics) will have additive or potent ing effects with SUBLIMAZE fentanyl. When patients have ceived such drugs, the dose of SUBLIMAZE fentanyl required be less than usual. Likewise, following administration SUBLIMAZE fentanyl the dose of other CNS depressant dru should be reduced.

SUBLIMAZE fentanyl should be administered with caution patients with liver and kidney dysfunction because of the imp tance of these organs in the metabolism and excretion of drug

SUBLIMAZE fentanyl may produce bradycardia, which m be treated with atropine; however, SUBLIMAZE fentanyl sho be used with caution in patients with cardiac bradyarrhythmias

When SUBLIMAZE fentanyl is used with a tranquilizer such INAPSINE droperidol, hypotension can occur. If this occurs t possibility of hypovolemia should also be considered and ma aged with appropriate parenteral fluid therapy. Repositioning t patient to improve venous return to the heart should be co sidered when operative conditions permit. Care should be ex cised in moving and positioning of patients because of t possibility of orthostatic hypotension. If volume expansion w fluids plus other countermeasures do not correct hypotension, t administration of pressor agents other than epinephrine should considered. Because of the alpha-adrenergic blocking action INAPSINE droperidol, epinephrine may paradoxically decrea the blood pressure in patients treated with INAPSINE droperid

Adverse Reactions As with other narcotic analgesics, the m common serious adverse reactions reported to occur w SUBLIMAZE fentanyl are respiratory depression, apnea, musc lar rigidity, and bradycardia; if these remain untreated, respirat arrest, circulatory depression or cardiac arrest could occur.

Other adverse reactions that have been reported are hy tension, dizziness, blurred vision, nausea, emesis, laryngospas and diaphoresis.

When a tranquilizer such as INAPSINE droperidol is used w SUBLIMAZE fentanyl, the following adverse reactions can occ chills and/or shivering, restlessness, and postoperative hallucir tory episodes (sometimes associated with transient periods mental depression); extrapyramidal symptoms (dystonia, akat sia, and oculogyric crisis) have been observed up to 24 ho postoperatively. When they occur, extrapyramidal symptoms c usually be controlled with antiparkinson agents. Postoperati drowsiness is also frequently reported following the use INAPSINE droperidol.

Overdosage ***Manifestations:*** The manifestations of SUBLIMAZ fentanyl overdosage are an extension of its pharmacologic actio ***Treatment:*** In the presence of hypoventilation or apnea, oxyg should be administered and respiration should be assisted controlled as indicated. A patent airway must be maintained; oropharyngeal airway or endotracheal tube might be indicated depressed respiration is associated with muscular rigidity, intravenous neuromuscular blocking agent might be required facilitate assisted or controlled respiration. The patient should carefully observed for 24 hours; body warmth and adequate flu intake should be maintained. If hypotension occurs and is seve or persists, the possibility of hypovolemia should be consider and managed with appropriate parenteral fluid therapy. A speci narcotic antagonist such as nalorphine, levallorphan, or naloxo should be available for use as indicated to manage respirat depression. This does not preclude the use of more immedia countermeasures. Consult the package insert for the individu narcotic antagonists for details about use.

How Supplied SUBLIMAZE® (fentanyl) injection is supplied ir cc. (**NDC** 0045-0180-03) and 5 cc. (**NDC** 0045-0180-05) ampuls, packages of 12.

IMPORTANT: Complete dosage information is available in ins which accompanies each package (or on request). The drug is ava able only upon direction of a physician.
U.S. Patent No. 3,164,600

• 9/

McNEIL McNeil Laboratories, Inc.
Fort Washington, Pa. 19034

CLASSIFIED ADVERTISING

ANESTHESIOLOGIST, D.D.S., wishes to associate with physician, a group, or staff position in a hospital, outpatient clinic or surgicenter. Completing two-year residency at a University Medical Hospital in July 1976. Contact Box 3-76-B, c/o I.A.R.S.

ANESTHESIOLOGIST needed for southwestern New Hampshire community. A new 220-bed facility with well equipped anesthesia department. Board eligible or board certified anesthesiologist with at least three years experience to join an anesthesiologist and CRNAs. Competitive salary and liberal fringe benefits. Send curriculum vitae and inquiries to Box 3-76-A, c/o I.A.R.S.

OBSTETRICAL ANESTHESIOLOGIST, Board eligible or certified with sub-specialty training, to head division of Obstetric Anesthesiology at rank of instructor or Assistant Professor. Responsibilities to include patient care and teaching, with research opportunities. An equal opportunity, affirmative action employer. Please send c.v. to James R. Harp, M.D., Dept. of Anesthesiology, Temple University School of Medicine, 3401 North Broad St., Phila., Pa. 19140.

ANESTHESIOLOGIST, 31, DOUBLY BOARDED (ABA, ABIM), Director of anesthesia education, Director of cardiac anesthesia at Bethesda. Leaving the Navy July 1976 and exploring all options. Offers carefully considered. R. Kravetz, M.D., 11748 Cherry Grove Drive, Gaithersburg, Maryland 20760.

FACULTY POSITIONS

Department of Anesthesiology, University of Louisville School of Medicine, has faculty positions open for board certified/eligible anesthesiologists. One position reserved for those with special interest in obstetrical anesthesia; work involves teaching, research and/or coordination of clinical activities. Send inquiries and curriculum vitae to K. P. Geevarghese, M.D., P.O. Box 1055, Louisville, Kentucky 40201. An equal opportunity, affirmative action employer.

ADMINISTRATIVE-TEACHING POSITION WANTED: CRNA with seven years clinical, teaching and administrative experience, plus masters degree. Prefer teaching hospital and authority equivalent to responsibility. Salary important, not hours. For resumé contact: Box 3-76-C in care of I.A.R.S.

PEDIATRIC ANESTHESIOLOGY RESIDENCY

Childrens Hospital of Los Angeles

Three-phase program: Clinical, Academic, Investigative, emphasizing practical aspects of anesthesiology related to infants and children.

AMA approval for third-year residency. Positions available from two months to one year.

Apply: George B. Lewis, Jr., M.D.
Head, Division of Anesthesiology
Childrens Hospital of Los Angeles
4650 Sunset Boulevard
Los Angeles, California 90054
Phone (213) 660-2450, Ext. 2262

POSITION WANTED BY CRNA: Experience and masters degree. Seeks position as director of nurse anesthesia school or division. Resumé on request. Reply: Box 3-76-D in care of I.A.R.S.

ANESTHESIOLOGY—66-man medical group located next to modern, accredited 480-bed hospital seeks Board Certified anesthesiologist to join two associates. Located in upper midwest university metropolitan area of 105,000; 35 minutes from superb clean lake region; associated with four-year medical school, teaching opportunities available; salary open; all specialties represented; will pay travel expenses for physician and spouse for interview. Write Box 11-75-A in care of I.A.R.S.

FACULTY POSITIONS

Department of Anesthesiology, Charity Hospital, New Orleans, affiliated with LSU and Tulane Medical Schools, has three faculty positions open for board certified/eligible anesthesiologists at Associate-Assistant Professor, Instructor levels. Duties involve teaching, research, clinical supervision. Salaries negotiable. Send inquiries and curriculum vitae to: M. Naraghi, M.D., Director, Department of Anesthesiology, Charity Hospital, New Orleans, Louisiana 70140.

NEBRASKA Opportunity for Anesthesiologist in 450-bed acute care, teaching hospital affiliated with two medical schools; must be board certified or eligible, salary commensurate with education and experience. An equal opportunity employer. Contact J. J. Matoole, M.D., Chief of Staff, Veterans Administration Hospital, 4101 Woolworth Avenue, Omaha, Nebraska 68105. (402) 346-8800, Ext. 442.

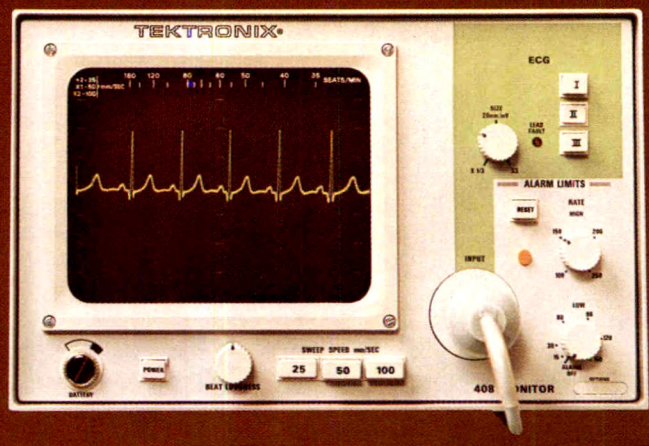
Rates for classified advertising are $3.00 per line, minimum 5 lines. Box number ads $3.50 per line. Classified Display rates on request. Copy deadline 6 weeks prior to publication. Do not submit payment with order; invoices will be sent for payment prior to publication. Ad copy, subject to acceptance by publisher, should be mailed to: Anesthesia and Analgesia . . . Current Researches, 3645 Warrensville Center Rd., Cleveland, Ohio 44122.

ECG monitoring doesn't have to be expensive – or complicated. For only $1500, the six simplified functions of TEKTRONIX 408 Monitor give you instantaneous ECG display, as well as every important feature for ECG monitoring during general anesthesia:

Three lead selection • Direct heart rate reading • High and low rate alarms • Adjustable waveform size control • Three selectable sweep speeds • Audible QRS tone • AC or internal battery operation • Price includes all accessories for ECG.

If you would like more information or a demonstration of the 408 or other TEKTRONIX Portable Patient Monitors, simply *call collect:* (503) 644-0161, Extension 6510.

The $1500 Portable ECG Monitor from Tektronix



TEKTRONIX®
committed to technical excellence

P.O. Box 500 Beaverton, Oregon 97077

PRECISE, ECONOMICAL, SAFE...

RALS POWER UNIT

...INSTANT ATOMIZATION FOR FAST TOPICAL ANESTHESIA

Fast, measured topical anesthesia is ready at your finger tips in a Rals Power Unit. Forget about pumping bulbs, uneven atomization, and limited spraying duration. The Rals Power Unit uses a non-toxic propellant, dichlorodifluoromethane (freon) to activate standard DeVilbiss Atomizers No's. 151, 152 and 163. Instantly, a fine mistlike spray is produced. A graduated solution vial is available for measuring the amount of solution administered.

The Rals Power Unit has been proven effective in cocainization prior to endotracheal intubation, endoscopic instrumentation, laryngotracheal insufflation, and in a variety of nose and throat procedures.

Rals Power Unit #168 are supplied six to a box with adaptor top and metal base. Illustration shows #152 atomizer. All styles in stock.

WRITE OR PHONE FOR LITERATURE, PRICE LIST.

RALS LABORATORIES DIVISION
SCHUEMANN Laboratories, Inc.
480 WEST AURORA ROAD • NORTHFIELD, OHIO 44067

SL-45

PROFESSIONAL INSTRUMENTS COMPANY MODEL NS-2 * PERIPHERAL NERVE STIMULATOR

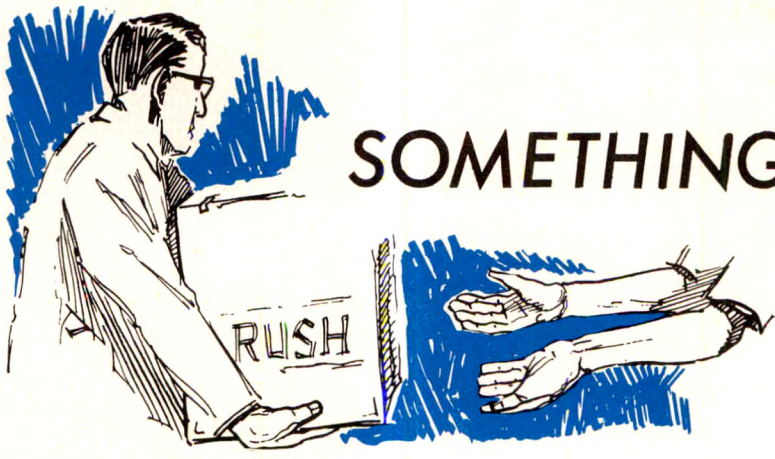
MONITORS EFFECTS OF SKELETAL MUSCLE RELAXANTS ON THE NEUROMUSCULAR JUNCTION, DETECTING ABNORMAL RESPONSE TO MUSCLE RELAXANTS AND DISTINGUISHES BETWEEN DEPOLARIZING AND NON-DEPOLARIZING BLOCKADE.

THE MODEL NS-2

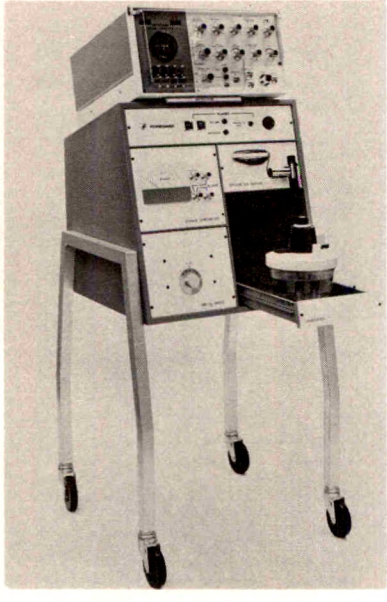
- ☐ **DELIVERS** STIMULI AT 5 SECOND INTERVALS. ONE OR FIFTY PULSES-PER-SECOND MAY BE SELECTED BY MOMENTARY PUSH-BUTTON SWITCHES.
- ☐ **OUTPUT** IS A MONOPHASIC SQUARE WAVE PULSE HAVING A RISE AND FALL TIME OF LESS THAN ONE MICROSECOND. AMPLITUDE OF PULSE IS LINEARLY ADJUSTABLE.
- ☐ **SOLID STATE**, RUGGED, BATTERY POWERED, PORTABLE AND LIGHTWEIGHT. THE USE OF INTEGRATED CIRCUITS ENSURES MAXIMUM RELIABILITY.
- ☐ **IT IS** THE RESULT OF AN AGGRESSIVE, CONTINUING RESEARCH AND DEVELOPMENT PROGRAM IN NERVE STIUMLATORS AND OTHER ELECTRONIC PRODUCTS BY PROFESSIONAL INSTRUMENTS COMPANY.

* MANUFACTURED UNDER U. S. DEVICE AND USE PATENT NO.'S 3,364,929 • 3,565,080 • 3,612,060 3,624,484 • 3,682,162

FOR INFORMATION, CONTACT: Professional Instruments Company
SUITE C5
4800 WEST 34TH ST.
HOUSTON, TEXAS 77018
PHONE (713) 681-1362



SOMETHING NEW

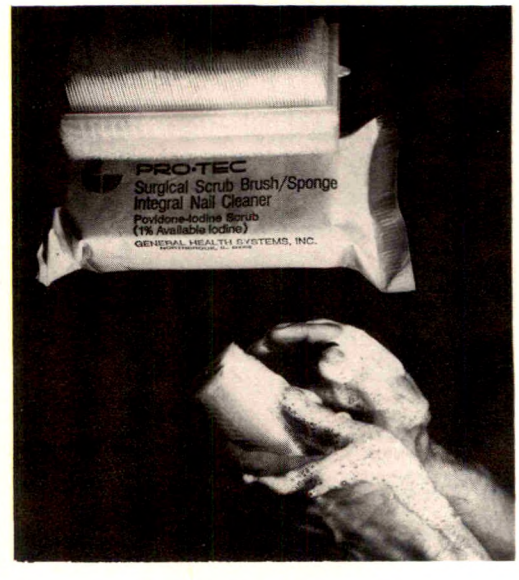


Air Products and Chemicals, Inc., Medical Products Division, Allentown, Pennsylvania, have a new volume ventilator called the FOREGGER® 210 Volume Ventilator.

It features an IMV (Inter-Mandatory Ventilation) function for weaning patients from mechanical ventilation and an I:E Ratio (Inspiratory:Expiratory) control that can be preset and maintained (1:1 to 1:4) over a variety of Tidal volumes and breathing rates. Other functions include PEEP, Assist, Inspiratory Pause, Sigh, and Multiple Sigh. A new high-output, minimal-noise compressor that fits between the ventilator's legs is available.

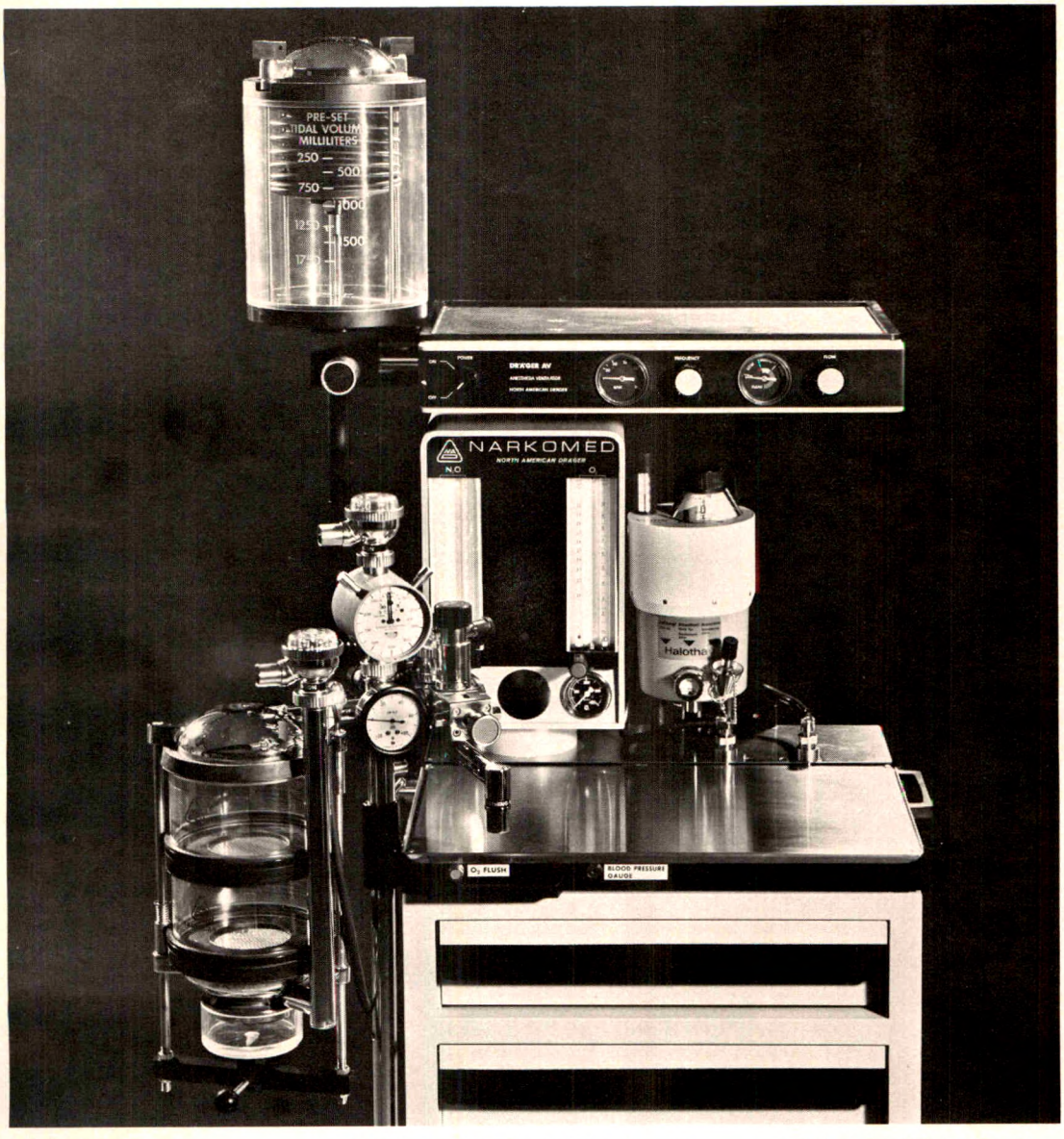
An extensive battery of audio and visual alarms designed to monitor the units' multi-functions, power-input and patient life-support systems is part of the new Foregger Ventilator.

★ ★ ★



General Health Systems, Inc., Northbrook, Illinois, have available the Pro-tec Disposable Scrub Brush and Sponge. Each scrub unit contains a bristle brush, foaming sponge and nail cleaner packaged in a tear-open pack.

NARKOMED



TOTAL ANESTHESIA SYSTEM

NARKOMED, a refreshing new concept in anesthesia machine design and styling, incorporating a contemporary anesthesia dispensing system with a built-in fluidic anesthesia ventilator and the widest variety of options.

Please return the accompanying coupon for further information.

NORTH AMERICAN DRÄGER

P.O. BOX 121, TELFORD, PENNSYLVANIA 18969

NORTH AMERICAN DRÄGER

P.O. Box 121
Telford, Pa. 18969

____ Please send information on the NARKOMED TOTAL ANESTHESIA SYSTEM
____ Please include a copy of Anesthesia Accessories Catalog
____ Please send information on _____

NAME _____

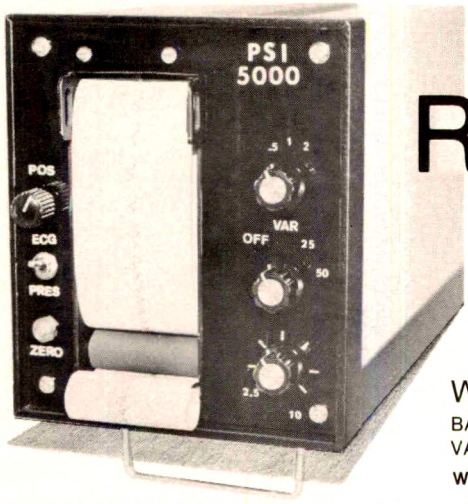
TITLE _____

HOSPITAL _____

ADDRESS _____

STATE _____ ZIP _____

INTRODUCING



the PSI 5000 Recorder

MEASURES & RECORDS

ECG • PULSE •
VITAL PRESSURES

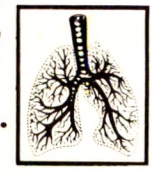
- ARTERIAL
- VENOUS
- INTERCRANIAL
- PULMONARY WEDGE

WHEN VERSATILITY COUNTS

BATTERY OPERATION, VARIABLE AMPLITUDES
VARIABLE SPEEDS AND TREND - 2.5 to 50 mm/Sec.

Whenever precise permanent copies are essential.

The PSI 5000 Recorder is a portable, battery operated, self-contained unit for use in most heart, lung, and blood pressure measurements. The PSI 5000 meets AHA specifications for electrocardiography, assuring superior performance in any application requiring high frequency response. The pen stylus is held in a stress-free mount on a titanium arm to provide exceptional life. It is capable of sustaining up to 1000 G's acceleration. A fully charged battery will provide up to four hours continuous operation.

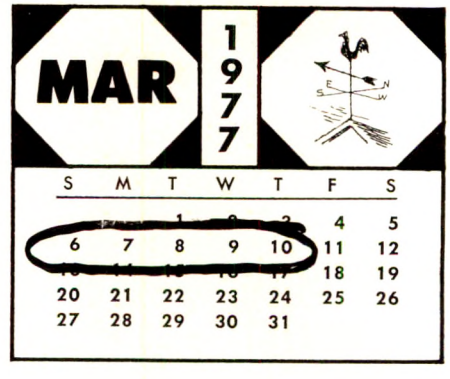


Pulmonary Specialties, Inc.

231 COMMERCE DRIVE, LARGO, FLORIDA 33540 • TELEPHONE (813) 585-4772

MARK

YOUR CALENDAR



51ST CONGRESS

International Anesthesia Research Society

MARCH 6-10, 1977

DIPLOMAT RESORT AND COUNTRY CLUBS
HOLLYWOOD, FLORIDA

Minute by minute

In those places where new concepts are readily accepted and fresh ideas in medical science generated, the BOC Medishield Wright Respiration Monitor is established as an important aid to health care. In the progressive environment of the theatre and ICU, the Wright Respiration Monitor has gained immediate acceptance.

The output of the Monitor can be connected to external recording apparatus. This trace of tidal and minute volumes provides information of diagnostic value. Therefore, the innovation enhances the value of apparatus as an aid to the investigation of patterns of respiration – of individual patients – and as a research tool of general application.

Features include:

Direct read-out of minute volume.

Mobility of Monitor. Choice of battery or mains supply.

Remote from point of measurement. Distant continuous monitoring.

Convenient, clearly labelled push-button controls.

Clear precise display of information – instantaneously assimilated.

Versatility – Safety – Reliability

BOC Medishield

Medishield (Harlow) Limited
Elizabeth Way, Harlow,
Essex CM19 5AB, England
Telephone: Harlow (0279) 29692
Cables: Britoxygen Harlow,
Telex: 81497
In Canada
Medishield Products Limited
In USA
Harris Lake Inc

☐ Please send me full descriptive literature on the Wright Respiration Monitor

☐ Please call me to arrange an appointment

Name _____

Position _____

Hospital _____

Address _____

ANA _____

INDEX OF ADVERTISERS

Air Products and Chemicals, Inc.—*Trace Gas Monitor* ..... (64)
Allergan Pharmaceuticals—*Lacri-Lube*® ..... (11)
American Optical, Medical Division—*Fiber Optic Laryngoscope* ..... (32), (33)
Applied Medical Research Corporation—*Dinamap* ..... (19)
Ayerst Laboratories—*Fluothane*® ..... (40), (41), (42)
BOC Medishield Ltd.—*Wright Respiration Monitor* ..... (59)
Burroughs Wellcome Co.—*Anectine*® ..... (30), (31)
Cincinnati Sub-Zero Products, Inc.—*Blanketrol*® ..... (61)
Concept, Inc.—*Anesthesia Products* ..... (48)
Dupaco, Inc.—*Anesthesia Apparatus* ..... (27)
Dupaco, Inc.—*Blood Pressure Cuffs* ..... (48)
J. H. Emerson Company—*Emerson Relaxaid*(TM) ..... (63)
Endo Laboratories—*Narcan*® ..... (24), (25), (26)
Fenwall Laboratories—*Operating Room System* ..... (43), (44), (45), (46)
Harris-Lake, Inc.—*Anesthesia Equipment Catalog* ..... (2)
McNeil Laboratories, Inc.—*Innovar*® ..... (17), (18)
McNeil Laboratories, Inc.—*Sublimaze*® ..... (50), (51), (52)
Medical and Industrial Equipment Div., Claudius Ash, Inc.—
Jackson-Rees T-Piece ..... (49)
Medical Management Company—*Management Services* ..... (61)
Medsonics, Inc.—*Versatone*(TM) *Doppler* ..... (39)
National Catheter Corp.—*Catheters* ..... (28), (29)
North American Drager—*Narkomed Anesthesia System* ..... (57)
Ohio Medical Products—*Disposable Endotracheal Tubes* ..... (47)
Ohio Medical Products—*Ethrane*® ..... (8), (9), (10)
O'Neal, Jones & Feldman, Inc.—*Antilirium* ..... (20)
Organon, Inc.—*Pavulon*® ..... (21), (22), (23)
Pfizer Laboratories—*Vistaril*® *I.M.* ..... (12), (13), (14)
Pharmaseal—*Stylox* ..... (62)
Professional Instruments Co.—*Peripheral Nerve Stimulator* ..... (55)
Pulmonary Specialties, Inc.—*PSI 5000 Recorder* ..... (58)
A. H. Robins Co., Inc.—*Dopram*® ..... (6), (7)
Royal Victoria Hospital—McGill University—
1976 Review Course in Anaesthesia ..... (61)
Schuemann Labs (Rals Div.)—*Rals Power Unit* ..... (55)
Tektronix, Inc.—*Medical Monitor* ..... (54)

212-978-6900 516-546-5511

800-645-2059

MEDICAL MANAGEMENT CO.

A National Organization — Established 1946

COLLECTIONS • DATA PROCESSING • MANAGEMENT •

All Third Party Claims Processed

Home Office

76 Pine Street Freeport, N.Y. 11520

McGILL UNIVERSITY

ANNUAL REVIEW COURSE IN ANAESTHESIA - 1976

May 24-28, 1976

This course is directed towards senior residents, candidates preparing for higher examinations and full time specialist anesthesiologists. The course content has been chosen to review important areas of scientific background and clinical practice, with emphasis on recent developments.

Teaching personnel consist of senior members of the McGill Faculty of Medicine together with a most distinguished guest faculty.

The meeting is held in a relaxed and attractive setting in McGill University.

FEE: $200.00
$100.00 (residents)

For further details write to:

The Secretary
Post-Graduate Board
Royal Victoria Hospital
687 Pine Avenue, West,
Montreal H3A 1A1, Quebec

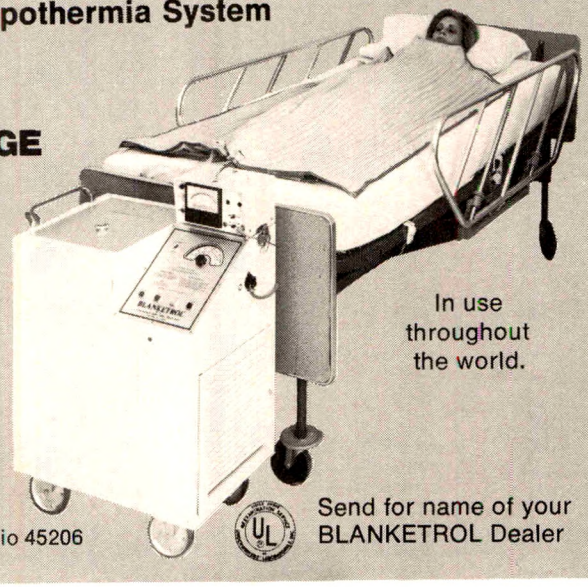
BLANKETROL®

Hyper-Hypothermia System

***SAME* BIG VALUE**

***NEW* SMALL PACKAGE**

Simple two step operation
Accurate and dependable performance
Exclusive safety features
Field serviceable



In use throughout the world.

CINCINNATI SUB ZERO PRODUCTS INC.

2612 Gilbert Avenue, Cincinnati, Ohio 45206

Send for name of your BLANKETROL Dealer

Back pressure stops here.

Our new Stylox™ anesthesia medication device, with its special ratchet plunger design, is all it takes to stop back pressure.

No more tiresome disconnecting syringes from I.V. lines, or worrying about check valves, slide clamps and tubes. . . .

Plus, the ratchet design lets you precisely inject incremental doses.

Stylox. It makes your work a whole lot easier. Send for sample now.

O.R./ANESTHESIA PRODUCTS BY
PHARMASEAL®
GLENDALE, CALIFORNIA 91201

Send me a Stylox™ sample.

Name _____

Hospital _____

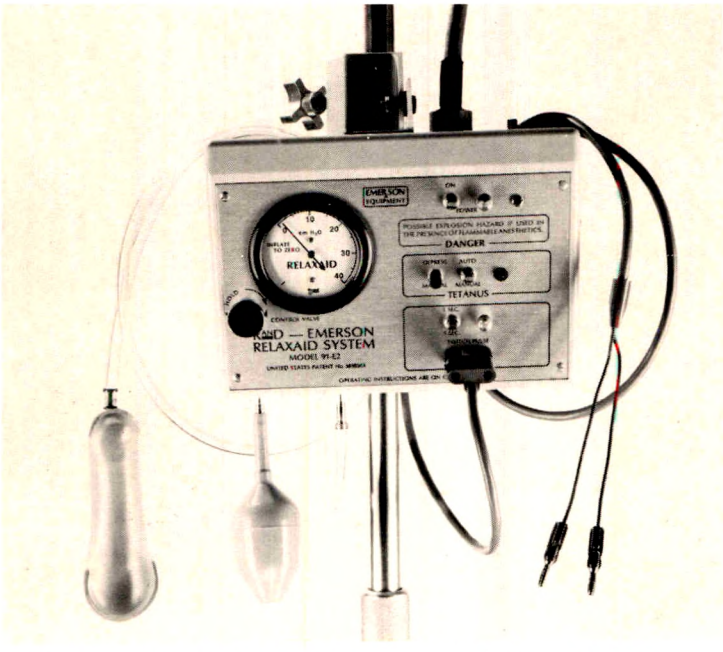
Address _____

City _____ State _____ Zip _____

(Clip out and mail to Pharmaseal,
1015 Grandview Ave., Glendale, CA 91201)

AA-3

R AND D-EMERSON RELAXAID™



for CORRECT RELAXANT DOSAGE—
AVOIDANCE OF OVERDOSE—
PROMPT RECOVERY—

The stimulator is programed to deliver pulses, through electrodes, to the ulnar nerve. A flexible pneumatic bulb is placed in the patient's hand, with his fingers held against it by tape. The bulb is then air-filled to a pressure of 20 cm. H_2O. As the fingers flex, even slightly, compression of the bulb is registered on an aneroid gauge. The pattern of these responses keeps the anesthetist informed of the relaxant's effectiveness.

The more precise monitoring provided by the RELAXAID™ enables relaxant levels to be kept adequate but without overdose. During recovery the RELAXAID™ shows the return of strength to the patient's muscles.

Please request Form 91-E2

J. H. EMERSON COMPANY
CAMBRIDGE, MASSACHUSETTS 02140

If You're Confused About O.R. Pollution, Cut It Out.

Get a compilation of data on the problems of trace anesthetic gas and OR pollution control. Send for our Positive Response Program.

Besides reports and studies to help you put the problem in perspective, our "PRP" plan of action provides an up-to-date look at our products which help you detect and scavenge trace gas in your OR. Key to our program is the Foregger 410 N_2O Trace Gas Monitor, a basic requirement for any efficient trace gas monitoring program. It's designed to provide rapid and continuous sampling of the OR air you breathe.

The machine has two sensing modes—Monitor (0-100 ppm) and Leak Test (0-1,000 ppm). The first mode continuously monitors the ambient air through the gas inlet of the machine. The second permits probing of local concentrations and sounds a repetitive burst alarm as the gas concentration increases.

In short, the Foregger 410 N_2O Trace Gas Monitor is a logical first step in solving your OR pollution problem. And there's more. The Scaveng-OR™ Gas Evacuator System, the Protect-OR™ Filter, Wall Suction Systems, and Air-CARE™ Preventive Maintenance Service.

Based on current data, it's likely that routine monitoring of pollution levels and scavenging of waste anesthetic gases will soon be standard Operating Room procedure. We're ready to help you now.

Fill out this ad coupon or ask our Representative for a Foregger PRP Folder. You'll get the problem in perspective and a plan of action to help correct it.

Air Products
FOREGGER

Yes, I am interested in minimizing my O.R. pollution problem. And I want a plan to help correct it. Send me your plan of action.

(Please print or type)

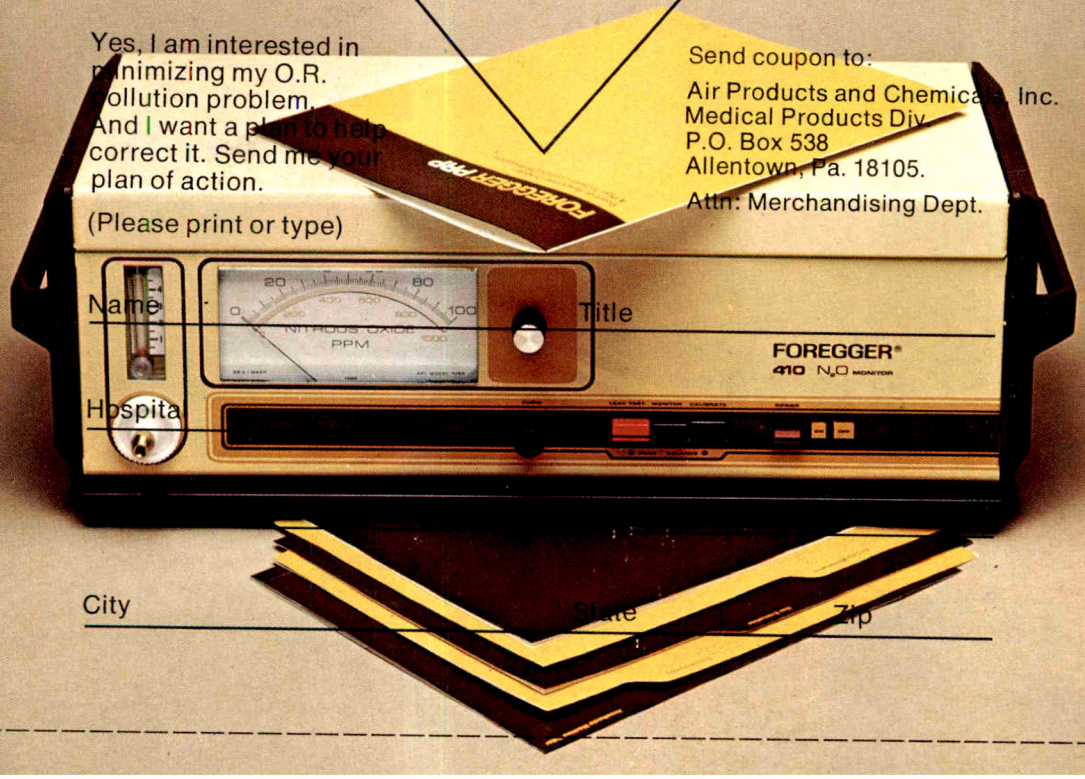
Name _____ Title _____

Hospital _____

City _____ State _____ Zip _____

Send coupon to:

Air Products and Chemicals, Inc.
Medical Products Div.
P.O. Box 538
Allentown, Pa. 18105.
Attn: Merchandising Dept.



Rec.
22.3.77

Anesthesia AND Analgesia

.....CURRENT RESEARCHES

Outpatient Evaluation: A New Role for the Anesthesiologist ..... Page 307

The Lateral Sitting Position for Neurosurgery ..... Page 326

Table of Contents ..... Page (4)

Oldest Publication in the Specialty - Established 1922

Journal of the International Anesthesia Research Society

Volume 55, No. 3 May-June, 1976

51st Congress

Hollywood, Florida - March 6-10, 1977

Harlake® laryngoscopes

personalized stainless steel

All Sizes of:

Macintosh
Miller
Harlake Modified Miller
Wisconsin

Polished exterior surface—peel proof

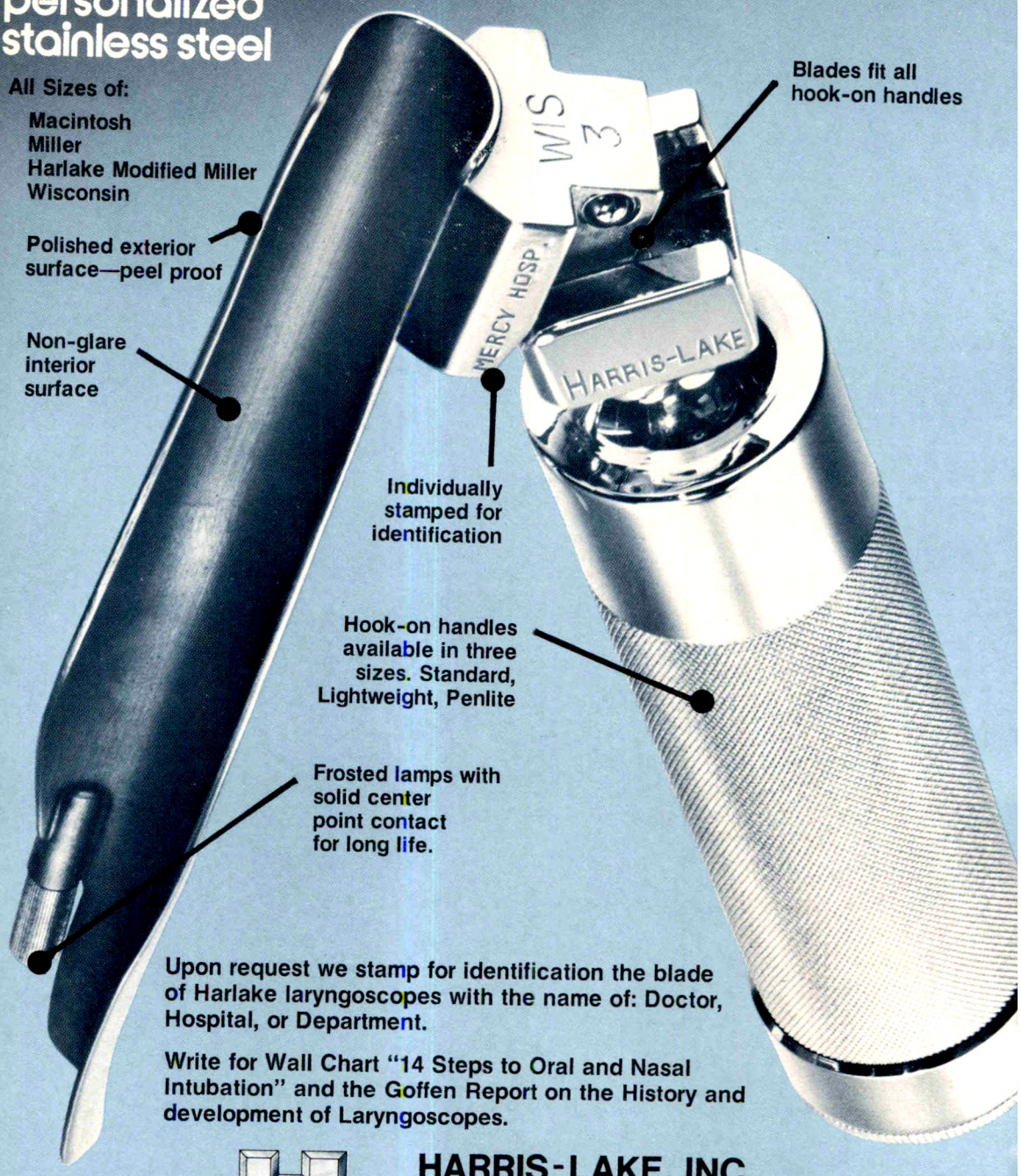
Non-glare interior surface

Blades fit all hook-on handles

Individually stamped for identification

Hook-on handles available in three sizes. Standard, Lightweight, Penlite

Frosted lamps with solid center point contact for long life.



Upon request we stamp for identification the blade of Harlake laryngoscopes with the name of: Doctor, Hospital, or Department.

Write for Wall Chart "14 Steps to Oral and Nasal Intubation" and the Goffen Report on the History and development of Laryngoscopes.

HARRIS-LAKE, INC.
10910 Briggs Road, Cleveland, Ohio 44111
Telephone (216) 251-8870
Telex: 98-5454

A Medishield Company Medishield

Anesthesia AND Analgesia ...CURRENT RESEARCHES

JOURNAL OF THE INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

3645 Warrensville Center Road • Cleveland, Ohio, U.S.A. 44122 • Telephones: (216) 295-1124, 295-1130

EDITORIAL BOARD

Editor: T. H. Seldon, M.D., Rochester, Minnesota

Associate Editors:
John T. Martin, M.D., Toledo, Ohio
Emerson A. Moffitt, M.D., Halifax, Nova Scotia
Dean H. Morrow, M.D., Houston, Texas
Edwin S. Munson, M.D., Gainesville, Florida
Robert K. Stoelting, M.D., Indianapolis, Indiana

Contributing Editors:
Douglas B. Craig, M.D., Winnipeg, Manitoba
E. Paul Didier, M.D., Rochester, Minnesota
Ronald W. Dunbar, M.D., Atlanta, Georgia
Leonard C. Jenkins, M.D., Vancouver, British Columbia
David E. Longnecker, M.D., Charlottesville, Virginia
John J. Savarese, M.D., Boston, Massachusetts
N. Ty Smith, M.D., San Diego, California

ANESTHESIA AND ANALGESIA . . . Current Researches is published bimonthly by the International Anesthesia Research Society, a non-profit scientific and educational corporation of the state of Ohio. Members of the Board of Trustees of the Society are: Kenneth K. Keown, M.D., John T. Martin, M.D., Emerson A. Moffitt, M.D., Dean H. Morrow, M.D., Edwin S. Munson, M.D., B. B. Sankey, M.D., T. H. Seldon, M.D., Robert K. Stoelting, M.D. Emeritus Trustees are: Paul R. Dumke, M.D., Morris J. Nicholson, M.D.

EDITORIAL CORRESPONDENCE and manuscripts should be addressed to: **T. H. Seldon, M.D., Editor, Kahler East—Suite C, Rochester, Minnesota 55901, U.S.A. Telephone: (507) 288-8655.** (See "A Guide for Authors" for information concerning manuscript preparation.) Original articles accepted for publication, or papers presented at the Society's annual scientific meetings which are subsequently published in this Journal become the property of the International Anesthesia Research Society, publisher. Reproduction in whole or in part is not permitted except by written consent of the publisher and the author.

BUSINESS CORRESPONDENCE, including subscription and membership payments, single issue purchases, change of address notices, requests for membership applications, should be sent to: **B. B. Sankey, M.D., Executive Secretary and Business Manager, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122. Telephones: (216) 295-1124, 295-1130.**

SUBSCRIPTION RATE: $25.00 per year (6 issues), including postage.

MEMBERSHIP DUES: $25.00 per year, includes a subscription to the Journal. **Membership** available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine or other disciplines who are engaged either in active clinical practice of or research in anesthesiology. **Associate Membership** available to individuals certified, licensed or accredited in anesthesia-related professions (CRNA, ARIT, Physician Assistant). **Educational Membership** (two years for $25.00) available to interns, residents, students in nurse anesthesia and related training programs.

SINGLE ISSUES: $4.50 each for years beginning 1970; $3.00 for years 1954-1969; $2.00 for years 1928-1953. (See "Back Issues Available" or write to Cleveland business office for listing.)

REPRINTS: For single copies, write directly to senior author at address listed on title page. Quantity orders (minimum 100) processed through Cleveland business office, prices on request.

MAILING DATES: Journals mailed 25th of January, March, May, July, September and November. Second Class postage paid at Cleveland, Ohio.

CHANGE OF ADDRESS NOTICES: Send to Cleveland business office by first day of the above months to ensure correct addressing of Journals. Replacement copies of missing Journals will be furnished without charge only if original copy is returned by post office as undeliverable.

ADVERTISING: Rate sheets, including advertising clearance procedure, available from national advertising representative: Charles B. Slack, Inc., 6900 Grove Road, Thorofare, New Jersey 08086—Telephone: (609) 848-1000. Orders, contracts, reproduction materials, set copy and classified ad copy should be sent only to Cleveland office.

©1976, International Anesthesia Research Society.

Contents

Volume 55 May-June, 1976 Number 3

SCIENTIFIC ARTICLES

OUTPATIENT EVALUATION: A NEW ROLE FOR THE ANESTHESIOLOGIST—Frost 307

ARTERIAL HYPOXEMIA CAUSED BY INTRAVENOUS KETAMINE—Zsigmond, Matsuki, Kothary and Jallad 311

FACTORS AFFECTING A-aDo_2 AFTER OPEN-HEART SURGERY—Sari, Okuda, Takeshita and Oda 315

HEPATIC CLEARANCE OF LIDOCAINE DURING N_2O ANESTHESIA IN DOGS—Burney and DiFazio 322

THE LATERAL SITTING POSITION FOR NEUROSURGERY—Garcia-Bengochea, Munson and Freeman 326

INSPIRED AIR TEMPERATURE WITH IMMERSION HEATER HUMIDIFIERS—Geevarghese, Aldrete and Patel 331

CLINICAL INVESTIGATION OF A NEW INTRAVENOUS ANESTHETIC—ETOXADROL HYDROCHLORIDE (CL-1848C; U-37862A)—Frederickson, Longnecker and Allen 335

ENDOBRONCHIAL INTUBATION FOR INTRAOPERATIVE PROTECTION OF A SINGLE FUNCTIONING LUNG: A CASE REPORT—Brodsky, Abramawitz and Mehrez 340

PROLONGED NEUROMUSCULAR BLOCKADE WITH PANCURONIUM IN THE PRESENCE OF ACUTE RENAL FAILURE: A CASE REPORT—Geha, Blitt and Moon 343

UNRELENTING HYPOTENSION ASSOCIATED WITH AN ACUTE ABDOMEN IN A COMATOSE HEMOPHILIAC CHILD: A CASE REPORT—Vaughan, Wilson and Waldbaum 346

AN UNUSUAL COMPLICATION OF LUMBOSACRAL PLEXUS BLOCK: A CASE REPORT—Muravchick and Owens 350

PROLONGED NEUROMUSCULAR BLOCKADE ASSOCIATED WITH TRIMETHAPHAN: A CASE REPORT—Wilson, Miller, Wright and Hasse 353

MEDICAL STATISTICS II. HOW OFTEN DID THAT HAPPEN?—Harris 357

THE EFFECT OF ENFLURANE, ISOFLURANE, FLUROXENE, METHOXYFLURANE AND DIETHYL ETHER ANESTHESIA ON OUABAIN TOLERANCE IN THE DOG—Ivankovich, Miletich, Grossman, Albrecht, El-Etr and Cairoli 360

THOUGHTS ABOUT MEDICAL WRITING. XXXV. "LET'S CALL IT HEBETIZATION"—Roland 366

AN EVALUATION OF MEMORY UNDER REGIONAL ANESTHESIA WITH IV LORAZEPAM AS A PREMEDICANT—Taub and Eisenberg 368

ANALYSIS OF TASKS AND HUMAN FACTORS IN ANESTHESIA FOR CORONARY-ARTERY BYPASS—Kennedy, Feingold, Wiener and Hosek 374

ANESTHETIC CONSIDERATIONS FOR PERICARDECTOMY IN UREMIC PERICARDIAL EFFUSION—Konchigeri and Levitsky 378

EFFECT OF ISOPROTERENOL AND PROPRANOLOL ON HALOTHANE MAC IN DOGS—Tanifuji and Eger 383

Anesthesia AND Analgesia . . . Current Researches

SCIENTIFIC ARTICLES—May-June, 1976 (Continued)

CIRCULATORY RESPONSES AND HALOTHANE CONCENTRATIONS DURING GASTRIC OR GALLBLADDER TRACTION WITH AND WITHOUT NEUROMUSCULAR BLOCKADE—Stoelting, Peterson and Madura 388

LARYNGOTRACHEAL RESIDUE DURING ENDOTRACHEAL ANESTHESIA—Lee and Gildea 392

BUTORPHANOL AND MORPHINE: A DOUBLE-BLIND COMPARISON OF THEIR PARENTERAL ANALGESIC ACTIVITY—Tavakoli, Corssen and Caruso 394

NITROUS OXIDE ENCEPHALOGRAPHY: 5-YEAR EXPERIENCE WITH 475 PEDIATRIC PATIENTS—Elwyn, Ring, Loeser and Myers 402

THE EFFECT OF GENERAL ANESTHETIC AGENTS, OUABAIN, AND ALDOSTERONE ON STRIATED MUSCLE CONTRACTION IN TOAD—Amaranath and Andersen 409

METHOXYFLURANE BIOTRANSFORMATION AND RENAL FUNCTION FOLLOWING METHOXYFLURANE ADMINISTRATION FOR VAGINAL DELIVERY OR CESAREAN SECTION—Young, Stoelting, Bond and Peterson 415

50th CONGRESS REPORT 420

CASE HISTORY NUMBER 90: CARDIAC DECOMPENSATION DURING ENFLURANE ANESTHESIA IN A PATIENT WITH MYOTONIA ATROPHICA—Meyers and Barash .. 433

BRIEF REPORTS

DEFECTIVE DISPOSABLE ENDOTRACHEAL TUBE—Chiu and Meyers 437

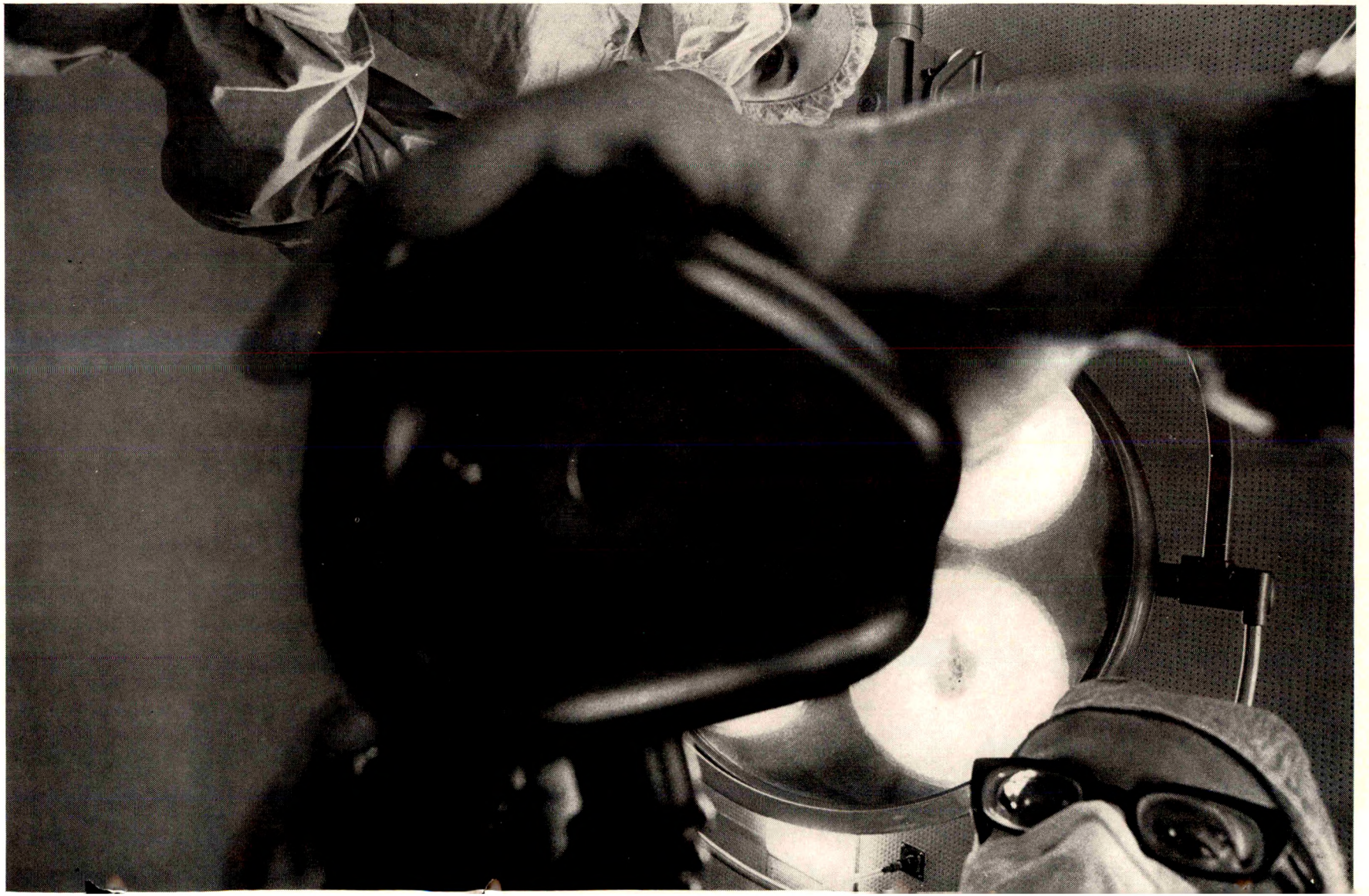
FATAL COMPLICATION FROM SWALLOWED DENTURE FOLLOWING PROLONGED ENDOTRACHEAL INTUBATION: A CASE REPORT—Kroesen and Haid 438

HYPERCAPNIA DURING CYCLOPROPANE ANESTHESIA: A CASE REPORT—Barasch, Booth and Modell 439

CALIBRATION OF THE NARKOTEST® GAS MONITOR FOR ISOFLURANE—Velazquez and Feingold 441

FEATURES

People and Places ..... (15)
We Salute, Paul R. Dumke, M.D. 443
Correspondence 445
Editor's Choice 455
The Physician and The Law 459
Questions and Answers 460
Book Review 465
Scientific Articles, Next Issue ..... (35)
A Guide for Authors ..... (36)
Back Issues Available ..... (38)
Classified Advertising ..... (48)
Something New ..... (54)
Index of Advertisers ..... (69)



In 16 years of use in the United States, FLUOTHANE (halothane) has been administered over 100 million times in a wide variety of surgical procedures. 100 million . . . extensive usage and evaluation that attests to FLUOTHANE as the most widely used inhalant anesthetic.

Since it was first introduced, over 4,000 papers worldwide have been published, ranging from review articles to in-depth studies. 4,000 papers . . . a bibliographic record of note on the most widely used inhalant anesthetic.

In a continuing program of informational services on anesthesiology, Ayerst provides printed and audiovisual aids reflecting the opinions and experiences of recognized authorities in the field. These include the highly regarded series on *Anesthesia Rounds* and *Clinical Aspects of Anesthesiology*, as well as several films of educational value—all available through your Ayerst Representative.

FLUOTHANE® (HALOTHANE) ...OVER 100 MILLION ADMINISTRATIONS

- nonflammable, nonexplosive
- permits use of high concentrations of oxygen
- allows free use of cautery for more adequate control of bleeding
- minimal odor facilitates smooth, rapid induction, reduces patient distress
- early obtundation of pharyngeal and laryngeal reflexes facilitates intubation
- lessens airway problems
- permits rapid adjustment of depth of anesthesia
- emergence is rapid and tranquil with quick recovery of protective reflexes
- minimal nausea and vomiting, shorter recovery room stay

Ayerst®

See last page of advertisement for prescribing information.

FLUOTHANE®

brand of halothane

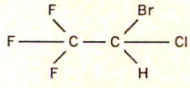
the most widely used inhalant anesthetic

from **Ayerst**

for precision, experience, quality, and service

(Complete text of package circular.)

Description. FLUOTHANE, brand of halothane, is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20° C., and the boiling point (range) is 49° C.-51° C. at 760 mm. Hg. The vapor pressure is 243 mm. Hg at 20° C. The blood/gas coefficient is 2.5 at 37° C., and the olive oil/water coefficient is 220 at 37° C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. FLUOTHANE is soluble in rubber, some plastics, and similar materials; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizing bottles not specifically designed for its use. It is recommended that vaporizers be emptied at the end of each operating day. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE should be avoided when a previous exposure was followed by fever and jaundice, or when there was an unexplained postoperative fever.

FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy: Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

Adverse Reactions. The following adverse reactions have been reported: hepatic necrosis, cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

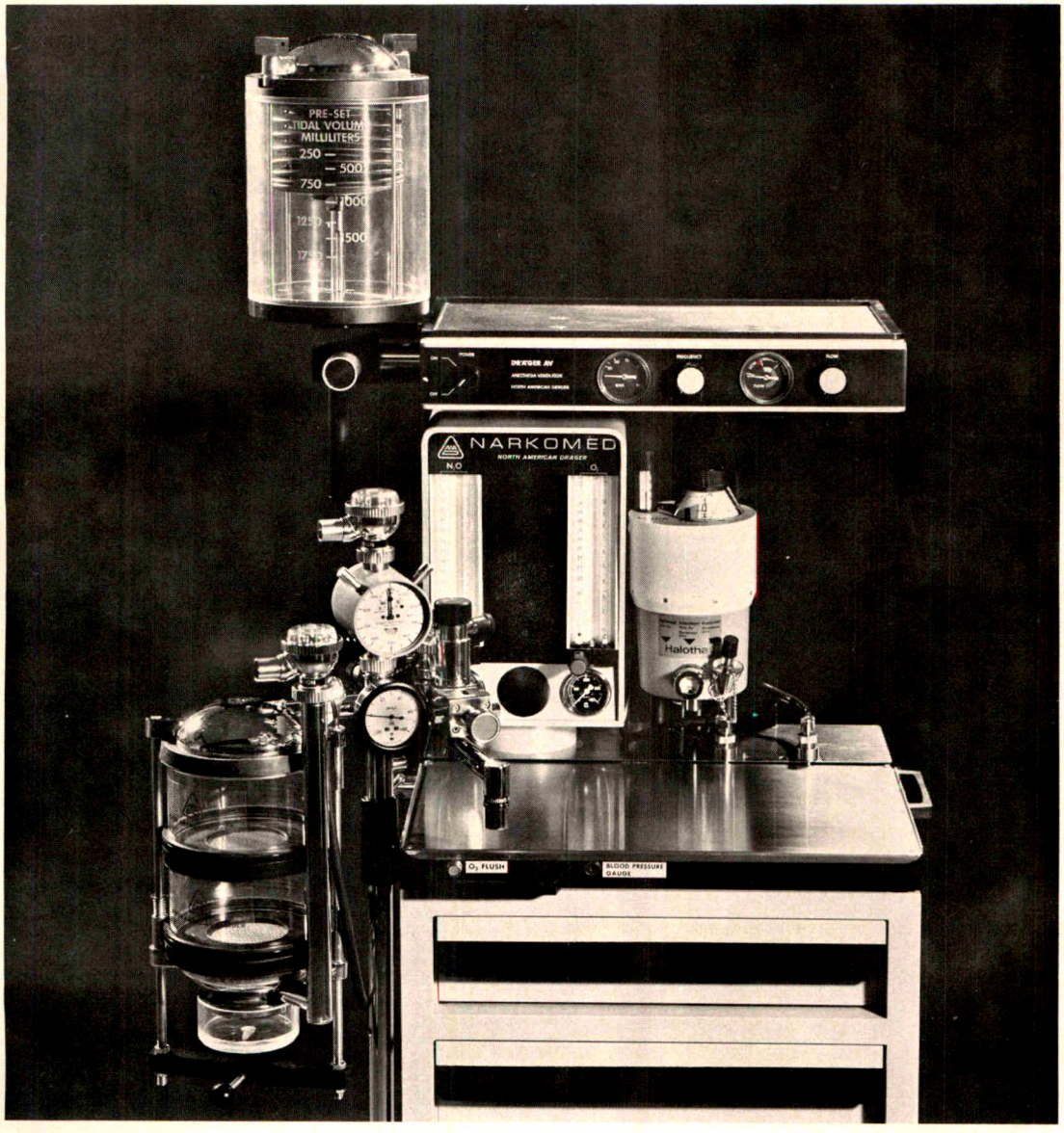
FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide (usually in a 50:50 ratio).

How Supplied. No. 3125—Unit packages of 125 cc. and 250 cc. of halothane stabilized with 0.01% thymol (w/w).

7522

Ayerst **AYERST LABORATORIES**
New York, N.Y. 10017

NARKOMED



TOTAL ANESTHESIA SYSTEM

NARKOMED, a refreshing new concept in anesthesia machine design and styling, incorporating a contemporary anesthesia dispensing system with a built-in fluidic anesthesia ventilator and the widest variety of options.

Please return the accompanying coupon for further information.

NORTH AMERICAN DRÄGER

P.O. BOX 121, TELFORD, PENNSYLVANIA 18969

NORTH AMERICAN DRÄGER

P.O. Box 121
Telford, Pa. 18969

____ Please send information on the NARKOMED TOTAL ANESTHESIA SYSTEM
____ Please include a copy of Anesthesia Accessories Catalog
____ Please send information on _____

NAME _____

TITLE _____

HOSPITAL _____

ADDRESS _____

STATE _____ ZIP _____

Nesacaine®
(Chloroprocaine Hydrochloride)

1% and 2% solution in 30-ml. multiple-dose vials

For Infiltration and Regional Anesthesia

Nesacaine®-CE
(Chloroprocaine Hydrochloride)

2% and 3% solution in 30-ml. single-dose vials

For Caudal and Epidural Anesthesia

INDICATIONS

NESACAINE in multiple dose vials and NESACAINE-CE in single dose vials without preservatives are indicated for production of local anesthesia by infiltration injection and nerve block.*

*NESACAINE in multiple dose vials with preservatives is not to be used for caudal or epidural anesthesia. NESACAINE-CE contains no preservatives and the unused portion must be discarded after initial use.

CONTRAINDICATIONS

NESACAINE and NESACAINE-CE are contraindicated in patients hypersensitive to drugs of the PABA ester group. Central nervous system disease is generally considered a contraindication to caudal or epidural nerve block.

WARNINGS

RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE IMMEDIATELY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED. As NESACAINE-CE contains no preservative, discard unused drug remaining in vial after initial use. Equipment and drugs necessary for the treatment of inadvertent intravascular injection, intrathecal injection, or excessive dosage should be immediately available.

Usage in Pregnancy: Safe use of chloroprocaine hydrochloride has not been established with respect to adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential unless in the judgment of the physician the potential benefits outweigh the unknown hazards. In obstetrics, if vasoconstrictor drugs are used either to correct hypotension or are added to the local anesthetic solution, the obstetrician should be warned that some oxytocic drugs may cause severe persistent hypertension and even rupture of a cerebral blood vessel may occur during the post partum period.

Solutions containing vasoconstrictors, particularly epinephrine and norepinephrine, should be used with extreme caution in patients receiving certain antidepressants such as MAO inhibitors, and tricyclic compounds since a severe prolonged hypertension may occur.

PRECAUTIONS

The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious undesirable systemic side effects. Tolerance varies with the status of the patient. Debilitated patients, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical status.

Solutions containing vasoconstrictors should be used cautiously in the presence of disease which may adversely affect the patient's cardiovascular system.

Chloroprocaine hydrochloride should be employed cautiously in persons with known drug allergies or sensitivities.

The decision whether or not to use local anesthesia in the following conditions depends on the physician's appraisal of the advantages as opposed to the risk:

Paracervical block when fetal distress is anticipated or when predisposing factors causative of fetal distress are present (i.e., toxemia, prematurity, diabetes, etc.). Injection of solutions containing epinephrine in areas where the blood supply is limited (i.e., ears, nose, digits, etc.) or when peripheral vascular disease is present.

ADVERSE REACTIONS

Adverse reactions result from high plasma levels due to rapid absorption, inadvertent intravascular injection or excessive dosage. Hypersensitivity, idiosyncrasy, or diminished tolerance are other causes of reactions. Reactions due to overdosage (high plasma levels) are systemic and involve the central nervous system and the cardiovascular system.

Reactions involving the central nervous system are characterized by excitation and/or depression. Nervousness, dizziness, blurred vision or tremors may occur followed by drowsiness, convulsions, unconsciousness and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestations may be drowsiness merging into unconsciousness and respiratory arrest.

Reactions involving the cardiovascular system include depression of the myocardium, hypotension, bradycardia and even cardiac arrest.

Treatment of a patient with toxic manifestations consists of maintaining an airway, and supporting ventilation using oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system consists of using vasopressors, preferably those that stimulate the myocardium (e.g., ephedrine) and intravenous administration in small increments of an ultrashort acting barbiturate (i.e., thiopental, thiamylal) or a short acting barbiturate if these are not available (secobarbital, pentobarbital) or a short acting muscle relaxant (succinylcholine), together with oxygen. Muscle relaxants and intravenous barbiturates should be used only by those familiar with their use.

Allergic reactions are characterized by cutaneous lesions, urticaria, edema and other manifestations of allergy. The detection of sensitivity by skin testing is of doubtful value.

DOSAGE AND ADMINISTRATION

The maximum single recommended doses of chloroprocaine hydrochloride are: without epinephrine, 800 mg.; with epinephrine (1:200,000), 1000 mg. The recommended dosage is based on requirements for the average adult and should be reduced for elderly or debilitated patients and children.

The recommended doses given below serve only as a guide to the amount of anesthetic required for most routine procedures.

1. INFILTRATION AND NERVE BLOCK (NESACAINE)

Type of Block	Volume	Concentration
Occipital	3-5 ml.	1%-2%
Mandibular	2-3 ml.	2%
Maxillary	2-3 ml.	2%
Infra-orbital	0.5-1 ml.	2%
Cervical	3-4 ml. (for each segment)	1%-2%
Brachial plexus	30-40 ml.	2%
Ulnar nerve	3-5 ml.	2%
Paravertebral	3-5 ml.	2%
Intercostal	3 ml.	1%-2%
Sciatic nerve	10-15 ml.	2%
Stellate ganglion	5-10 ml.	1%-2%
Lumbar sympathetic (1 needle technic)	15-20 ml.	1%-2%
Interdigital	3-4 ml. (without epinephrine)	1%-2%

Fractional doses, up to 300 to 600 mg., may be given at 50 minute intervals.

2. CAUDAL AND EPIDURAL BLOCK (NESACAINE-CE)

For *caudal anesthesia* the initial dose is 15 to 25 ml. of a 2% or 3% solution. Repeated doses may be given at 40 to 60 minute intervals.

For *epidural anesthesia* in the lumbar and sacral regions 2.0 to 2.5 ml. per segment of a 2% or 3% solution can be used. The usual total volume of Nesacaine-CE is from 15 to 25 ml. Repeated doses 2 to 6 ml. less than the original dose may be given at 40 to 50 minute intervals.

HOW SUPPLIED

Nesacaine is supplied as follows:

1% solution (10 mg/ml.) in 30 ml. multiple-dose vials, 12 vials per carton.

2% solution (20 mg/ml.) in 30 ml. multiple-dose vials, 12 vials per carton.

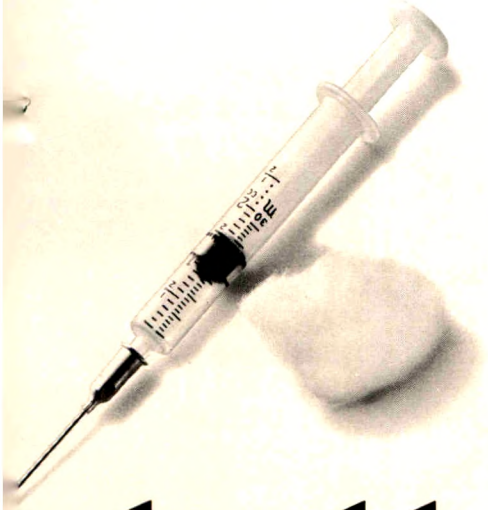
Nesacaine-CE is supplied as follows:

2% solution (20 mg/ml.) in 30 ml. single-dose vials, 12 vials per carton.

3% solution (30 mg/ml.) in 30 ml. single-dose vials, 12 vials per carton.

PENNWALT

Pennwalt Prescription Products
Pharmaceutical Division
Pennwalt Corporation
Rochester, New York 14603



A local anesthetic should meet your needs...

Rapid Onset of Action. Saves doctor, nurse and patient time.

Effective Anesthesia. Nesacaine (Chloroprocaine Hydrochloride) offers 80% to 90% pain-free procedures at recommended doses.

Exceptional Safety. Less potential for postoperative complications. Nesacaine is rapidly hydrolized in plasma, whereas lidocaine and other amide-type local anesthetics are metabolized in the liver. With Nesacaine, therefore, there is minimal potential risk of systemic toxicity, accumulation of metabolites, stimulation of CNS or cardiovascular effects.

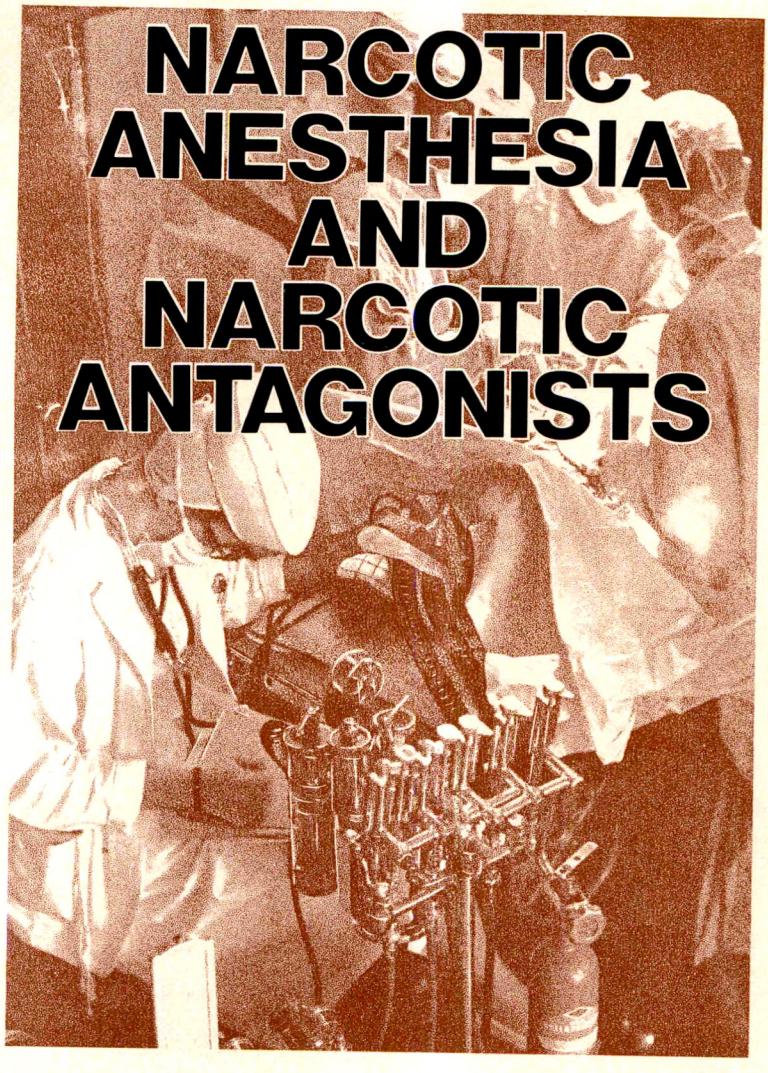
Excellent Penetration. Chloroprocaine's lipid solubility and ionization characteristics impart it with excellent penetration.

Minimal Irritation at Injection Site. Few patient complaints about procedural pain, little soreness and inflammation after procedure.

Rapid and Complete Wear-Off. No residual numbness, patient back to normal faster.

See opposite page for brief prescribing information.

Look into
Nesacaine®
(Chloroprocaine Hydrochloride)
It meets your needs.



NARCOTIC ANESTHESIA

- Despite many advantages, the use of opioids to supplement nitrous oxide anesthesia may be associated with significant postoperative depression.

NARCAN® (naloxone HCl)

- Narcan® in sufficient doses wil antagonize opioid effects, including all degrees of respiratory depression and analgesia.
- The degree of narcotic antagonism exhibited by NARCAN® is dose dependent

A recent study of surgical patients receiving narcotic-nitrous oxide anesthesia was undertaken to determine whether careful titration of naloxone would reverse post-operative narcotic depressior and maintain a subjective level of analgesia.[1]

THE OBJECTIVES:

- Restore consciousness
- Reverse narcotic-induced respiratory depression as evidenced by $PaCO_2$
- Maintain *subjective* analgesia

THE METHOD:

- 12 unpremedicated patients received INNOVAR® (fentanyl/droperidol) 5-10 ml I.V. followed by thiopental for induction. Anesthesia was maintained with N_2O-O_2. Increments of 0.1 mg *fentanyl* were given I.V. every 10 minutes during surgery.

Following the procedure, naloxone (0.1 mg/ml) was given in 0.1 mg I.V. increments at 1 minute intervals until the patient was awake, lucid and had adequate tidal and minute volumes. Additional naloxone

1. Heisterkamp DV, Cohen PJ: *Anesth Analg* (Cleve) 53:12-18, Jan-Feb 1974.

NARCAN® is an Endo registered U.S. trademark; U.S. Pat. 3,254,088

was given I.V. as needed in the first 6 patients; a second group of 6 patients received supplemental naloxone I.M. 30 minutes after the initial I.V. dose.

11 patients received 10 mg *morphine* I.M., as well as secobarbital and atropine, 1½ hours preoperatively. Anesthesia was induced by 30 mg morphine given slowly I.V. followed by thiopental and was maintained by N_2O-O_2. Additional morphine was given in divided increments to total 1 mg/kg in the first hour. Further morphine was given as needed. For initial narcotic reversal, naloxone was given as above except at 2 minute intervals. Supplemental naloxone was given I.M. 30 minutes later.

THE RESULTS (fentanyl group):

- When fentanyl was used as the sole narcotic supplement during anesthesia, an I.M. dose of naloxone equal to half the I.V. reversal dose and given ½ hour later provided adequate narcotic reversal.

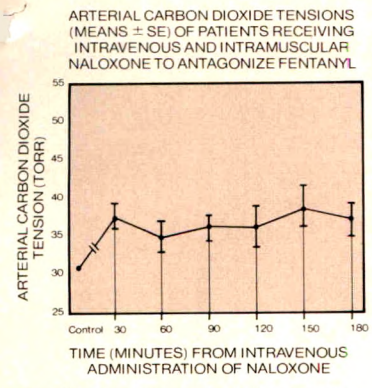


Fig. 1. Control and postoperative $PaCO_2$ in 6 patients receiving I.V. and I.M. naloxone following fentanyl.

THE RESULTS (morphine group):

- "After other narcotics, such as morphine, an I.M. dose of naloxone equal to the I.V. dose appears appropriate."

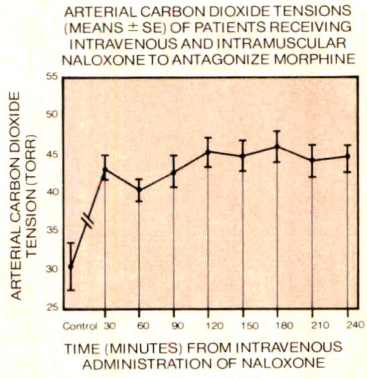


Fig. 2. Control and postoperative $PaCO_2$ in 11 patients receiving I.V. and I.M. naloxone following morphine.

THE CONCLUSIONS:

- "Naloxone provides fast, potent, and reliable antagonism to narcotic-induced respiratory depression."
- "By careful titration, this antagonism can be achieved while acceptable analgesia is maintained."
- "Both morphine and fentanyl groups had adequate analgesia, with only 2 patients [of total 21] requiring pain medication in the recovery room."

- **reverses all degrees of narcotic-induced respiratory depression**
- **does not cause narcotic-like effects**
- **does not augment non-narcotic depression**
- **acts rapidly—generally within 2 minutes following I.V. use and slightly less rapidly when given I.M.**
- **does not lead to tolerance**
- **does not produce psychotomimetic effects or pupillary constriction**
- **can be repeated if initial dose doesn't produce desired degree of narcotic reversal and improvement in respiratory function**
- **following satisfactory response patient should be observed closely and given repeat doses, if necessary, since the duration of action of some narcotics may exceed that of NARCAN®**

Please see next page for complete prescribing information.

Endo Laboratories, Inc.
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530
DUPONT

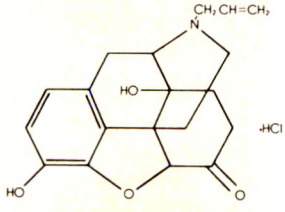
•restored consciousness
•reversed narcotic-induced respiratory depression
•maintained subjective analgesia

NARCAN®
(naloxone HCl)

can reverse narcotic-induced respiratory depression while maintaining subjective analgesia

NARCAN® (naloxone HCl)

DESCRIPTION NARCAN® (naloxone hydrochloride), a narcotic antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



NALOXONE HYDROCHLORIDE
(N-allyl-nor-oxymorphone HCl)

Naloxone hydrochloride occurs as slightly off-white crystals, and is soluble in water, slightly soluble in alcohol and practically insoluble in ether.

NARCAN® (naloxone hydrochloride) Injection is available in two concentrations, 0.02 mg and 0.4 mg of naloxone hydrochloride per ml. Each ml of either strength contains 8.6 mg of sodium chloride; and 2.0 mg of methylparaben and propylparaben as preservatives in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

ACTIONS NARCAN® (naloxone hydrochloride) is an essentially pure narcotic antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists; NARCAN® (naloxone hydrochloride) does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists it exhibits essentially no pharmacologic activity.

In the presence of physical dependence on narcotics NARCAN® (naloxone hydrochloride) will produce withdrawal symptoms; it has not been shown to produce tolerance nor to cause physical or psychological dependence.

When NARCAN® (naloxone hydrochloride) is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of NARCAN® (naloxone hydrochloride). Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of NARCAN® (naloxone hydrochloride), however, will also be dependent upon the amount, type and route of administration of the narcotic being antagonized.

INDICATIONS NARCAN® (naloxone hydrochloride) is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by natural and synthetic narcotics, propoxyphene and the narcotic-antagonist analgesic pentazocine.
NARCAN® (naloxone hydrochloride) is also indicated for the diagnosis of suspected acute opiate overdosage.

CONTRAINDICATIONS NARCAN® (naloxone hydrochloride) is contraindicated in patients known to be hypersensitive to it.

WARNINGS NARCAN® (naloxone hydrochloride) should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN® (naloxone hydrochloride) should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride).

NARCAN® (naloxone hydrochloride) is not effective against respiratory depression due to non-opioid drugs.

Usage in Pregnancy Safe use of NARCAN® (naloxone hydrochloride) during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or other embryotoxic effects (See ANIMAL PHARMACOLOGY AND TOXICOLOGY). However, NARCAN® (naloxone hydrochloride) should be administered to pregnant patients only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS In addition to NARCAN® (naloxone hydrochloride), other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

In an isolated report two patients with pre-existing ventricular irritability requiring lidocaine, and either isoproterenol or epinephrine for hypotension following cardiopulmonary bypass proced developed ventricular tachycardia or fibrillation when given NARCAN® (naloxone hydrochlori I.V. at 9 and 14 hours, respectively, postoperatively for persistent unresponsiveness. Althoug direct cause and effect relationship has not been established, NARCAN® (naloxone hydrochl should be used with caution in patients with cardiac irritability.

ADVERSE REACTIONS In rare instances nausea and vomiting have been reported in postoper patients receiving NARCAN® (naloxone hydrochloride) in doses higher than that recommende cause and effect relationship has not been established.

DOSAGE AND ADMINISTRATION NARCAN® (naloxone hydrochloride) may be administered intra ously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydroc ride) the patient should be kept under continued surveillance and repeated doses of NARCAN (naloxone hydrochloride) should be administered, as necessary.

USAGE IN ADULTS Narcotic Overdose—Known or Suspected The usual initial adult dose is (mg (1 ml) NARCAN® (naloxone hydrochloride) administered I.V., I.M. or S.C. If the desired deg of counteraction and improvement in respiratory function is not obtained immediately followi I.V. administration, it may be repeated intravenously at 2 to 3 minute intervals. Failure to obt significant improvement after 2 or 3 doses suggests that the condition may be due partly or c pletely to other disease processes or non-opioid drugs.

Post Operative Narcotic Depression For the partial reversal of narcotic depression following use of narcotics during surgery, smaller doses of NARCAN® (naloxone hydrochloride) are usua sufficient. The dose of NARCAN® (naloxone hydrochloride) should be titrated according to the patient's response. Excessive dosage of NARCAN® (naloxone hydrochloride) may result in sigr cant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or tachycardia.

For the initial reversal of respiratory depression, NARCAN® (naloxone hydrochloride) should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal i.e., adequate ventilation and alertness without significant pain or comfort.

Repeat doses of NARCAN® (naloxone hydrochloride) may be required within one to two hour in vals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

USAGE IN CHILDREN Narcotic Overdose—Known or Suspected The usual initial child dose i 0.01 mg/kg body weight given I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guideline. If necessary, NARCAN® (naloxone hydrochloride) can be dilute with sterile water for injection.

USAGE IN NEONATES Narcotic-induced depression The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines.

HOW SUPPLIED 0.4 mg/ml of NARCAN® (naloxone hydrochloride) for intravenous, intramuscu and subcutaneous administration.

Available in 1 ml ampuls in boxes of 10 and 100.

0.02 mg/ml of NARCAN® (naloxone hydrochloride) NEONATAL INJECTION for intravenous, intramuscular and subcutaneous administration.

Available in 2 ml ampuls in boxes of 10 and 100 ampuls.

ANIMAL PHARMACOLOGY AND TOXICOLOGY In the mouse and rat the intravenous LD_{50} is 150 mg/kg and 109 ±4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rat the LD_{50} (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats 3 weeks produced only transient salivation and partial ptosis following injections; no toxic effe were seen at 10 mg/kg/day for 3 weeks.

Reproductive studies including fertility, general reproductive performance, embryotoxicity, tera togenicity, and lactation did not show any abnormality in mice and rats at 10 mg/kg/day.

NARCAN® (naloxone hydrochloride) Ampuls
Stocked in Military Depot, NSN 6505-00-079-7867

Endo Laboratories, Inc.
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DUPONT

PEOPLE and PLACES

The Department of Anesthesiology, West Virginia University School of Medicine, is sponsoring a Continuing Medical Education activity, entitled "Anesthesia Update 1976," June 26, 1976, at Lakeview Country Club, Morgantown, West Virginia.

★ ★ ★

The Third Annual Symposium, "Anesthesia and the Geriatric Patient," sponsored by the Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri, will be held November 12, 13, 14, 1976, at the Marriott Motor Hotel, St. Louis, Missouri. For more information, write to: **Leonard W. Fabian, M.D.,** Department of Anesthesiology, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, Missouri 63110.

★ ★ ★

The Department of Anesthesiology at New York University Post-Graduate Medical School is offering its second annual continuing education course, "Current Trends in Clinical Anesthesia," on September 18 and 19, 1976.

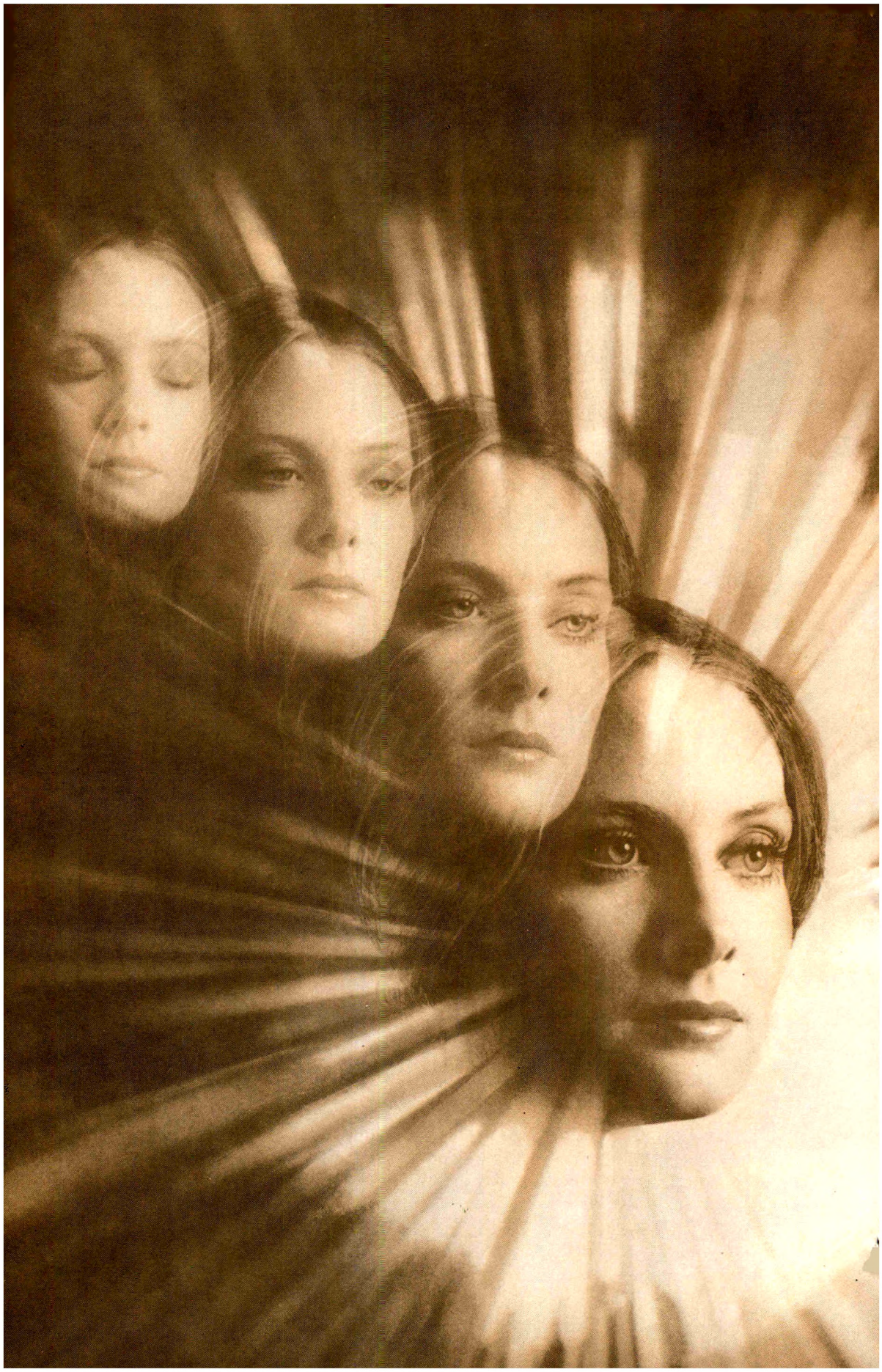
This course is designed to assist practicing anesthesiologists in updating clinical skills through theoretical and practical lectures and demonstrations.

For further information contact **Dr. James Cottrell,** Department of Anesthesiology, NYU School of Medicine, 550 First Avenue, New York, New York 10016.

★ ★ ★

Henry Knowles Beecher, MD, has been named the first recipient of an award for contributions to ethics and the life sciences established in his name by the Institute of Society, Ethics and the Life Sciences. Dr. Beecher is Henry Isaiah Dorr Professor of Research in Anaesthesia Emeritus at Harvard Medical School and a founding Fellow of the Institute.

The Henry Knowles Beecher Award for Contributions to Ethics and the Life Sciences will honor those whose careers have combined devotion to the highest ideals of scholarship and research with a dedication to ethical inquiry. It will be given at least once every five years but not more than once every two years.



A "quick recovery" anesthetic for short surgical procedures

Ethrane® (enflurane) fulfills your anesthetic requirements for short surgical procedures.

Fast Induction, Rapid Recovery. The low blood/gas partition coefficient of ETHRANE (1.91 at 37°C) assures rapid patient induction with minimal excitation. Its mild, pleasant odor is highly acceptable and ETHRANE does not stimulate increased salivation or affect bronchomotor tone.[1] Pharyngeal and laryngeal reflexes can be quickly and easily obtunded. Following anesthesia, because of its low blood solubility, ETHRANE is promptly eliminated at the lungs, permitting rapid emergence and recovery.[2]

Stable Cardiac Rhythm. Cardiac rhythm usually remains normal during ETHRANE anesthesia and is not altered even with elevations in arterial carbon dioxide.[3] Although nodal or atrial arrhythmias occasionally appear, ventricular extrasystoles are rare. Heart rate is sustained at preanesthetic levels. Bradycardia or tachycardia do not normally occur. Blood pressure tends to be reduced with induction, but this effect is reversed with surgical stimulation.[4]

Excellent Muscle Relaxation. At clinical concentrations, ETHRANE usually provides muscle relaxation sufficient for lower abdominal procedures. In addition, relaxation is often adequate for procedures of the upper abdomen. If greater relaxation is required, its potentiation of nondepolarizing relaxants reduces the dosage of such adjunctive neuromuscular blocking agents.[4]

Few Anesthetic Aftereffects. Following cessation of anesthesia with ETHRANE, recovery is rapid, uneventful, and complete. Postoperative return of adequate pulmonary ventilation is rapid.[1] Nausea, vomiting, and delirium are rare. Usually there is an early return of lucidity, desire for fluids, and generally a feeling of well-being.[1,5]

WARNING: Motor activity exemplified by movement of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia. For additional warnings, contraindications, and precautions, see following page.

Films Available for Medical Education. As a service to the anesthesia profession, Ohio Medical Products has available, without charge, motion pictures for use in continuing medical education. Topics include such areas as "Management of Ambulatory Surgical Procedures" and "The Use of ETHRANE." To arrange for a personal or group showing, contact your OHIO Anesthetic Representative, or write to our Communications Department in Madison, Wisconsin.

Ethrane®
(enflurane)

Versatile in Concept–Versatile in Performance

Ohio Medical Products
3030 AIRCO DRIVE
MADISON, WISCONSIN 53701

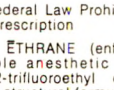
AIRCO®

See following page for full disclosure

Ethrane® (enflurane) Versatile in concept... Versatile in performance.

CAUTION: Federal Law Prohibits Dispensing without Prescription

Description: ETHRANE (enflurane) is a nonflammable anesthetic agent. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



Some physical constants of the compound are:

Molecular weight	184.5
Boiling point 760 mm Hg.	56.5°C
Refractive index n_D^{20}	1.3026-1.3030
Specific gravity 25°/25°C	1.517
Vapor pressure in mm Hg.**	20°C 174.5 25°C 217.7 36°C 345.2

**Equation for calculation of enflurane vapor pressures:

$$\log_{10} P = A + \frac{B}{T}$$

A = 7.967
B = −1678.4
T = °C + 273.16 (Kelvin)

Partition coefficients @ 37°C	
Water-gas	0.82
Blood-gas	1.91
Oil-gas	98.5
Partition coefficients @ 25°C— rubber and plastic	
Conductive rubber	74.0
Butyl rubber	90.0
Polyvinylchloride	120.0
Polyethylene	≈2.0
Polyurethane	≈1.5
Polyolefin	≈1.2
Butyl acetate	≈3.0
Solubility of enflurane in H_2O at 22°C	0.275%
Solubility of H_2O in enflurane	0.13%
Purity by gas chromatography	>99.9%
Flammability in air	None
Flammability in oxygen (Entire concentration range to saturation at 71 and 113°F and 743 mm Hg. pressure.)	None
M.A.C. (Minimum alveolar concentration)	
Man with pure oxygen	1.68
Man with 70% nitrous oxide	0.56 (est.)

ETHRANE is a clear, colorless, stable liquid without added chemical stabilizers. ETHRANE has a mild, sweet odor. Storage of samples in indirect sunlight in clear, colorless glass for a five year period, as well as direct exposure for 30 hours to a 2 amp, 115 V., 60 cycle long wave U.V. light, produced no changes in composition detectable by gas chromatography. ETHRANE in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed none of the alkali, indicative of strong base stability. ETHRANE does not decompose in contact with soda lime. ETHRANE does not attack aluminum, tin, brass, iron or copper.

Actions: ETHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ETHRANE are rapid. ETHRANE does not appear to stimulate excess salivation or tracheobronchial secretions, or affect bronchomotor tone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ETHRANE. ETHRANE reduces ventilation as depth of anesthesia increases. ETHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm. ETHRANE sensitizes the myocardial conduction system to epinephrine in dog and can produce serious arrhythmias. Comparable information in man is not available.

Muscle relaxation is adequate for intra-abdominal operation at normal levels of anesthesia. Should greater relaxation be necessary, minimal doses of muscle relaxants may be used. All commonly used muscle relaxants are compatible with ETHRANE. **The nondepolarizing muscle relaxants are markedly potentiated.** Neostigmine does not reverse the direct effect of ETHRANE.

Biotransformation of ETHRANE (enflurane) in man results in low levels of serum fluoride ions averaging 15 mM/L. These levels are well below the 50 mM/L seen to produce renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation.

Indications: ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

Contraindications: Seizure disorders (see WARNINGS).

Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.

Warnings: Increasing depth of anesthesia with ETHRANE (enflurane) produces a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by hyperventilation producing low arterial carbon dioxide tension. The pattern serves as a warning that depth of anesthesia is excessive. Cerebral blood flow and metabolism studies in normal volunteers during seizure patterns show no evidence of cerebral hypoxia, and recovery appears to be uncomplicated.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. With deep levels of anesthesia, more marked hypotension and respiratory depression are encountered.

The action of nondepolarizing relaxants is augmented by ETHRANE. Less than the usual amounts of these drugs should be used. The time for recovery from the myoneural effect of these relaxants is greater in the presence of ETHRANE than for other commonly used anesthetics.

The safety of the use of epinephrine topically and subcutaneously has not been established in man.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

Precautions: Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ETHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ETHRANE.

Adverse reactions: 1. Motor activity exemplified by movement of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia. 2. Hypotension and respiratory depression have been reported. 3. Arrhythmias, shivering, nausea, and vomiting have been reported. 4. Elevation of the white blood count has been observed. It has not been determined whether this is related to ETHRANE or to surgical stress.

Dosage and administration: The concentration of ETHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ETHRANE;
b) vaporizers from which delivered flows can easily and readily be calculated.

Maintenance concentration should not exceed 3%. Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ETHRANE and the heart rate remains constant. The use of anticholinergic drugs is a matter of choice.

Induction: Induction may be achieved using ETHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ETHRANE mixture. In general, inspired concentrations of 3.5-4.5% ETHRANE produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be attained with 1.5-3.0% concentration. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm range is preferred to hyper- or hypoventilation in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ETHRANE concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration; establish that the airway is clear and initiate assisted or controlled ventilation with pure oxygen as circumstances dictate.

Administration equipment: ETHRANE (enflurane) may be administered from a flow-through type vaporizer manufactured and specifically calibrated for ETHRANE. Vaporizers which deliver saturated vapor at reasonable flows but are not specifically calibrated for ETHRANE may be used.

ETHRANE contains no stabilizer. Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Packaging: ETHRANE (enflurane) is packaged in 125 and 250 ml. amber bottles. No additives or stabilizers are present.

References:

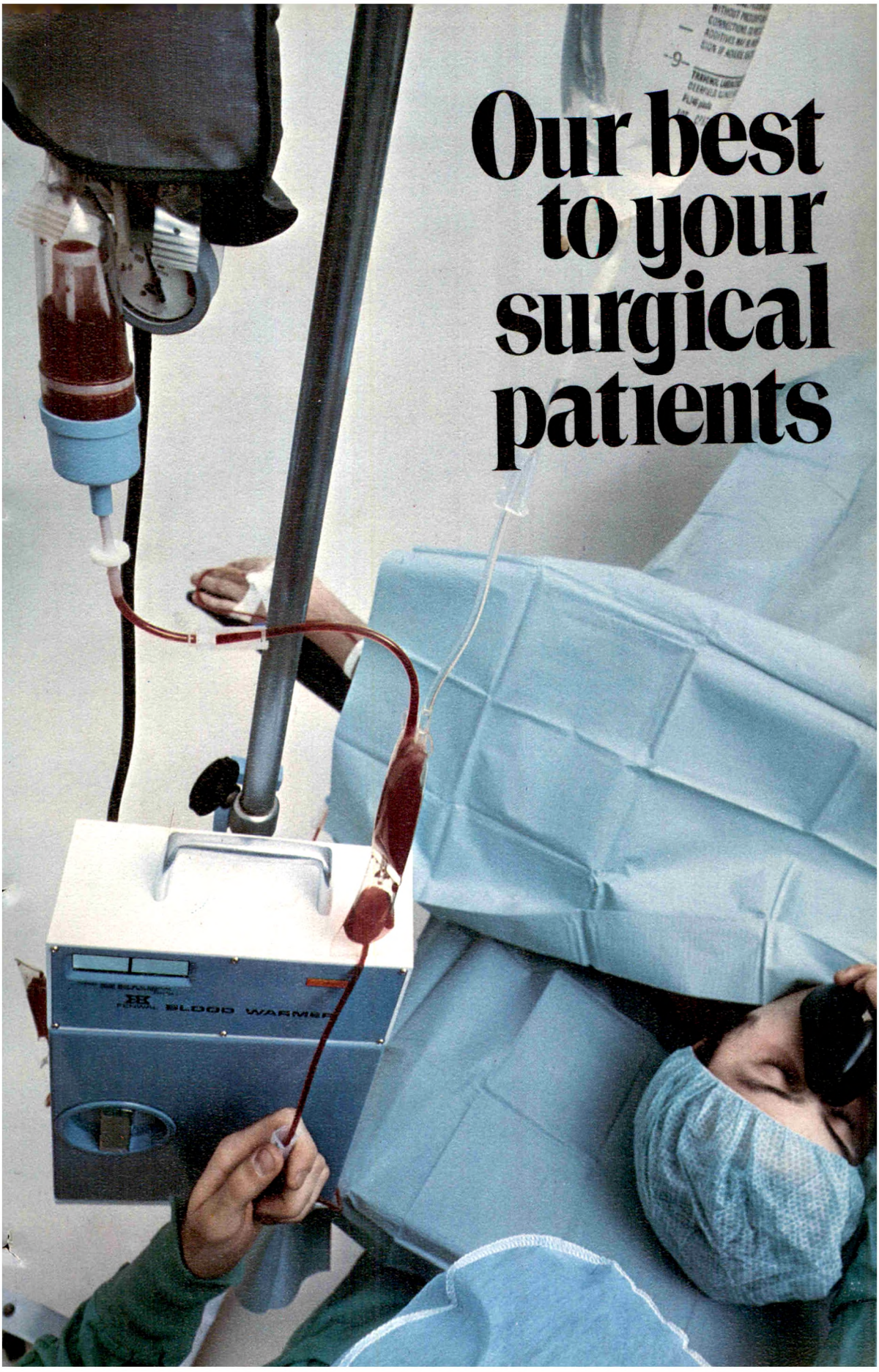
1. Dobkin, A. B., et al: Ethrane (Compound 347) Anesthesia: A Clinical and Laboratory Review of 700 Cases. Anesthesia and Analgesia **48**:477-494, May-June, 1969.

2. Torri, G., et al: Uptake and Elimination of Enflurane in Man. A Comparative Study between Enflurane and Halothane. British Journal of Anaesthesia. **44**:789-794, August, 1972.

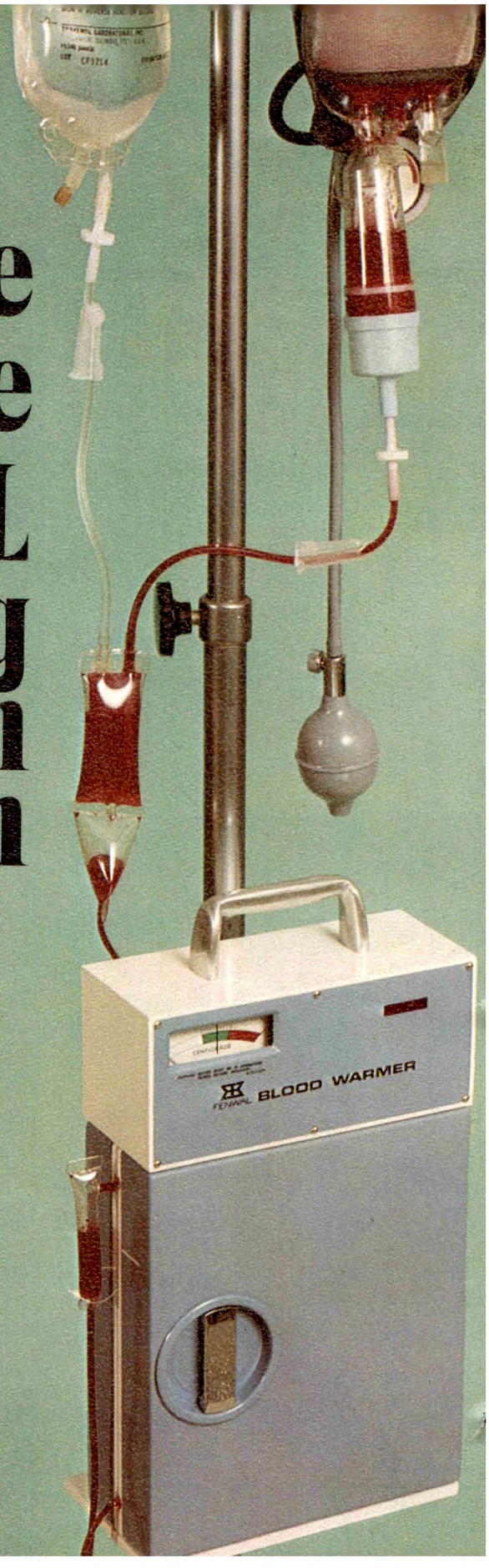
3. Marshall, B.E., et al: Some Pulmonary and Cardiovascular Effects of Enflurane (Ethrane) Anesthesia with Varying $PaCO_2$ in Man. British Journal of Anaesthesia. **43**:996-1002, November, 1971.

4. Botty, C., et al: Clinical Experiences with Compound 347, A Halogenated Anesthetic Agent. Anesthesia and Analgesia **47**:499-505, September-October, 1968.

5. Lebowitz, M.H., et al: Clinical Investigation of Compound 347 (Ethrane). Anesthesia and Analgesia. **49**:1-10, January-February, 1970.


Our best
to your
surgical
patients

The complete FENWAL operating room system



The Fenwal Dry Heat Blood Warmer is designed for use during single or multiple transfusions when precise regulation of blood temperature and flow rate is indicated. It utilizes a disposable plastic blood-warming pathway.

Fenwal Recipient Sets are available to accommodate your infusion requirements. The Single Lead Set is to be used for the intravenous administration of one unit of whole blood, red cells or plasma. The "Y" Recipient Set is designed to permit dual hookups for simultaneous administration of blood and/or solutions. The Triple Lead Set may be employed in multiple infusion procedures, i.e., blood, solutions, blood components and medication.

The Fenwal Microaggregate Blood Filter is designed to remove microaggregates down to 20 microns in size during intravenous administration of stored whole blood or red cells.

Fenwal Pressure Infusors provide an efficient non-air-dependent method for the rapid infusion of whole blood or red cells.

The Fenwal TYPENEX™ Blood Recipient Identification System ties together the identity of the transfusion candidate, his cross-match request form, blood sample and up to 10 cross-matched units of blood.

The Fenwal Venous Pressure Manometer Set is a disposable, preassembled unit that permits continuous monitoring of the patient's venous pressure while performing one simple hookup.

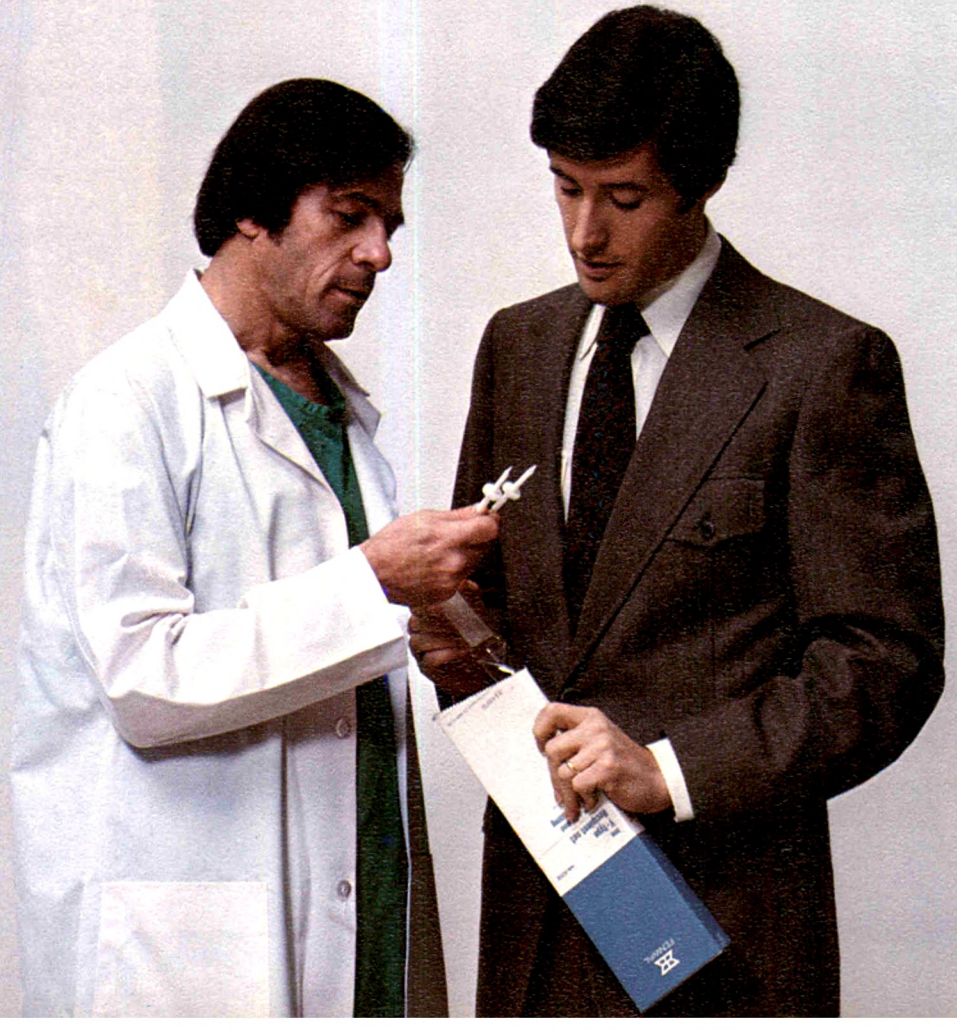
The Fenwal Platelet Recipient Set is designed specifically for the infusion of fresh blood and pool platelet concentrates.

Our best to you

Fenwal Laboratories has long been identified with innovation in modern blood handling systems. Our knowledge and experience in developing and providing sophisticated blood processing systems have earned a reputation for excellence. Thoroughly researched and tested to meet the demands of the medical profession, you can expect the same quality in Fenwal operating room devices that helped achieve our recognition with the nation's blood banks.

The Fenwal Specialist in your hospital can provide you and the other members of the operating team with completely detailed information on all of our products. Intensive training makes him fully qualified to answer your most involved questions regarding up-to-date blood transfusion procedure. Be sure to see your Fenwal Specialist the next time he visits your department.

FENWAL LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois, U.S.A. 60015.



INJECTION, equivalent to 10 mg metaraminol per ml

Aramine® (Metaraminol Bitartrate | MSD)

a vasopressor with positive inotropic effect

Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:
Effective: ARAMINE is indicated for prevention and treatment of the acute hypotensive state occurring with spinal anesthesia. Adjunctive treatment of hypotension due to hemorrhage; reactions to medications; surgical complications; and shock associated with brain damage due to trauma or tumor.
"Probably" effective: It may also be useful as an adjunct in the treatment of hypotension due to cardiogenic shock or septicemia.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Use should be avoided with cyclopropane or halothane anesthesia, unless clinical circumstances demand such use.

Precautions: Use with caution to avoid excessive blood pressure response. Rapidly induced hypertensive responses have been reported to cause acute pulmonary edema, arrhythmias, and cardiac arrest. Use with caution in digitalized patients, since the combination of digitalis and sympathomimetic amines is capable of causing ectopic arrhythmic activity. Treat cirrhotic patients cautiously; if diuresis ensues, restore electrolytes. Fatal ventricular arrhythmia has been reported in one patient with Laennec's cirrhosis. In several instances, ventricular extrasystoles that appeared during infusion have subsided promptly on reduction of infusion rate. Since metaraminol has prolonged duration of action, a cumulative effect is possible, leading to prolonged elevation of blood pressure even with discontinuation of therapy. Monoamine oxidase inhibitors have been reported to potentiate action of sympathomimetic amines.
When vasopressor amines are used for long periods, resulting vasoconstriction may prevent adequate expansion of circulating volume and may cause perpetuation of the shock state. Plasma volume may be reduced in all types of shock, and measurement of central venous pressure is the most useful means of assessing the adequacy of the circulating blood volume; blood or plasma volume expanders should be employed for hypotension or shock due mainly to decreased circulating volume. Because of its vasoconstrictor effect, metaraminol should be used with caution in heart or thyroid disease, hypertension, or diabetes. Sympathomimetic amines may provoke relapse in patients with history of malaria.

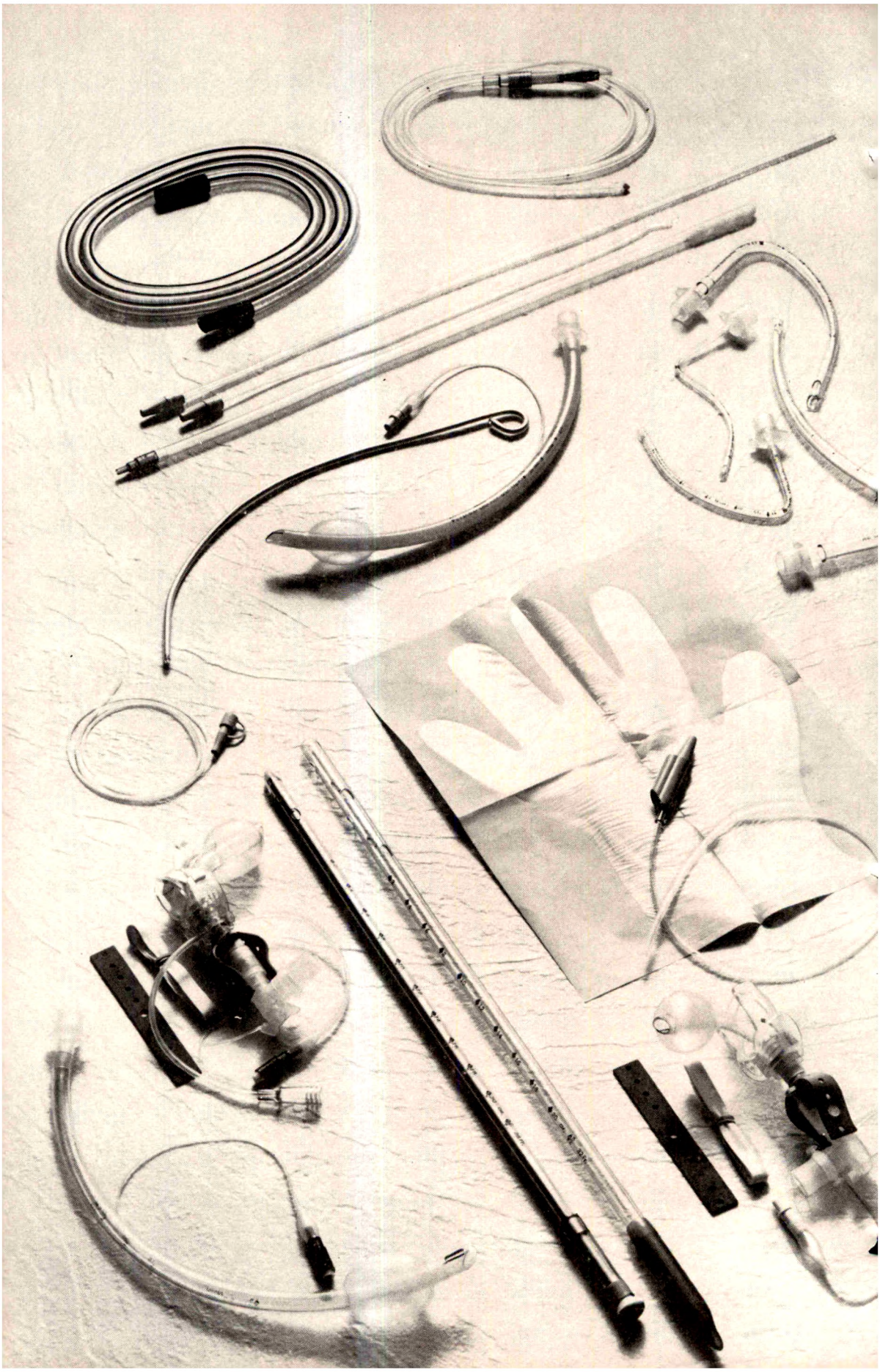
Adverse Reactions: Sinus or ventricular tachycardia, or other arrhythmias, especially in patients with myocardial infarction. Abscess formation, tissue necrosis, or sloughing may rarely follow use. In choosing the site of injection, it is important to avoid those areas recognized as *not* suitable for use of any pressor agent, and to discontinue infusion immediately if infiltration or thrombosis occurs. The larger veins of the antecubital fossa or the thigh are preferred to veins in the dorsum of the hand or ankle veins, particularly in patients with peripheral vascular disease, diabetes mellitus, Buerger's disease, or conditions with coexistent hypercoagulability.

Note: Response to vasopressors may be poor in patients with coexistent shock and acidosis. Established methods of shock management, such as blood or fluid replacement when indicated, and other measures directed to the specific cause of the shock state also should be used. *Only Sodium Chloride Injection or 5 percent Dextrose Injection should be used as a diluent.*

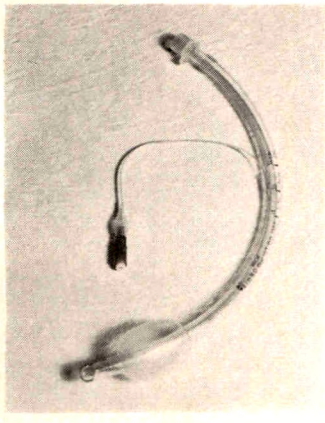
How Supplied: Injection, in 1-ml ampuls and 10-ml vials, containing per ml: metaraminol bitartrate equivalent to 10.0 mg metaraminol; inactive ingredients: sodium chloride, 4.4 mg; water for injection, q.s. ad 1.0 ml; and 0.15% methylparaben, 0.02% propylparaben, and 0.2% sodium bisulfite added as preservatives.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

MSD
MERCK SHARP & DOHME



National Catheter... we make lifelines.



hi-lo® tracheal tubes*

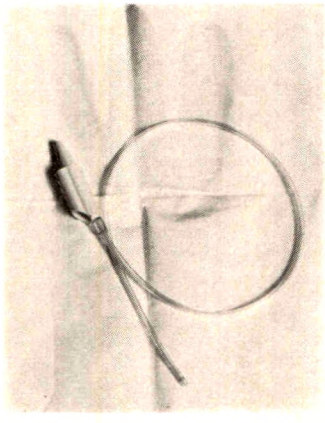
A high volume, low pressure cuffed endotracheal tube that inflates with a minimum of air pressure. Creates a no-leak seal, usually of less than 25 cm. H_2O; avoids trauma to the tracheal wall.

Soft and pliant tubes have a true murphy tip, intubate easily. Water clear, the tube fogs on exhalation, an instant monitor of patient respiratory function. May be used orally or nasally.

Other trademarks of NCC: **holdtite™, vari-form®, ventrol®, suture rib™, versi-cath®, maxi-flex & vac™, RAE™.**

*Covered under one or more of the following patents, U.S. Pat. No's 3,625,793, 3,605,750, 3,508,554, 3,610,242, and patents pending.

†University of Pittsburgh



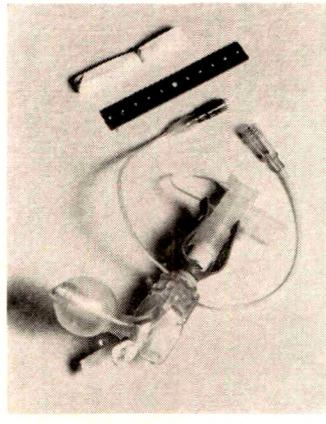
Ncc satin-cath™* & gluv set

This sterile, disposable gluv set has met with overwhelming acceptance.

The GENTLE-FLO® catheter has a SATIN-SLIP SURFACE™ that provides smooth, non-binding insertion into an endotracheal tube.

The paperbacked glove slips on easily, fits either hand and is easily removed when suctioning is complete. The set also contains a waterproof receptacle. Pull the marked tabs and it opens and locks in position, ready to use for the receipt of sterile water. Equipped with VACTROL® connector, catheter suction may be simply regulated from full on to off.

Available with catheters in all popular sizes. Packaged in a sterile peel-back paper pouch—50 sets/box.



pitt*† trach speaking tube

This speaking tube permits tracheostomy patients to converse. The emotional benefits are obvious.

The hi-lo® cuff inflates easily to avoid tracheal damage. This possibility is further removed because the clear tubing permits convenient bronchoscopic observation of the tracheal wall. The auxiliary air supply tube is to be connected to a humidified air oxygen outlet to achieve a speaking air flow.

Equipped with Eross Safety Straps and removable spacers and adjustable collar, the trach tube is adaptable to fit any adult patient. The suction port, which may be locked, allows for suctioning of the patient without removing the respirator and introducing a flexible fiberoptic bronchoscope, thus avoiding delays during this critical period.

Manufactured with the precision medicine must demand.

national catheter corp.

A Mallinckrodt® COMPANY

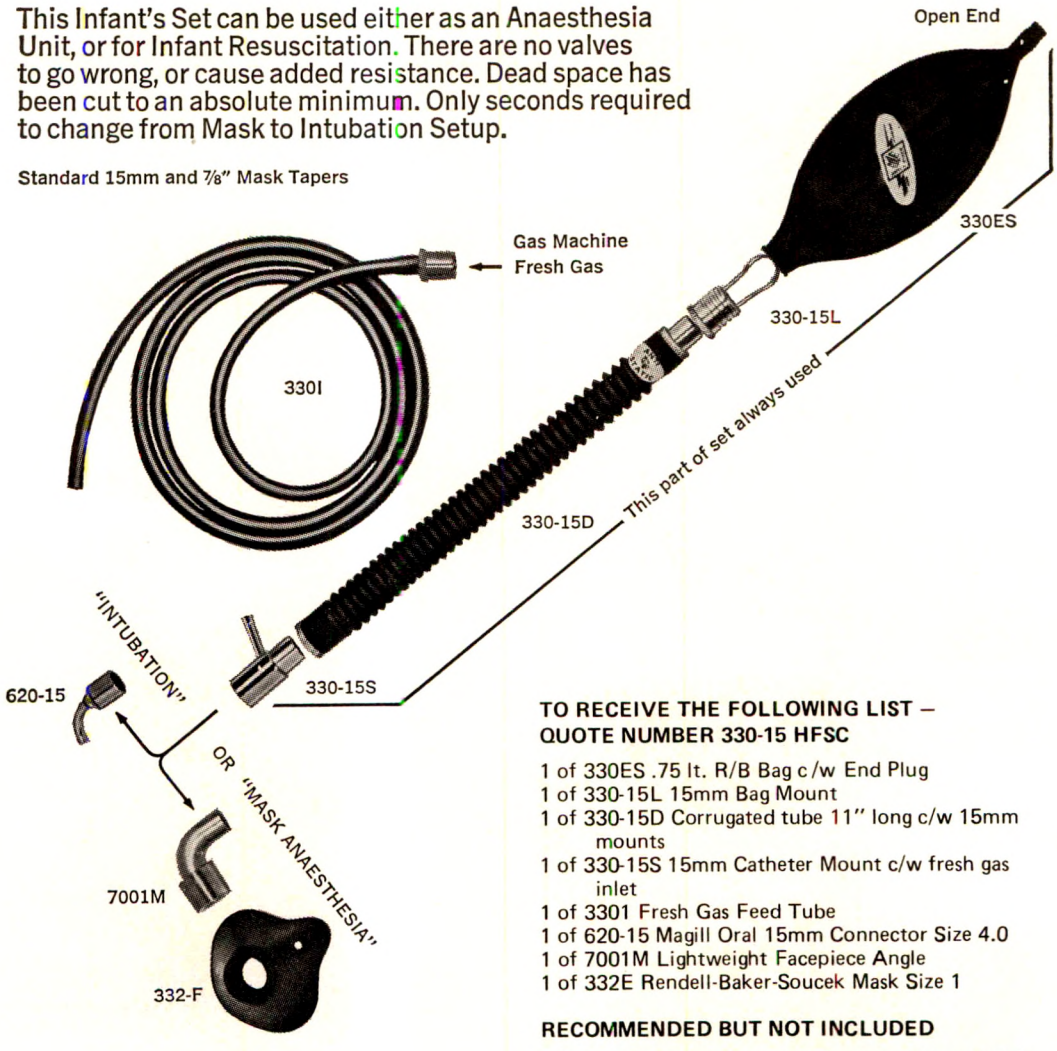
Home of the Sheridan Line of Catheters argyle new york 12809

JACKSON-REES MODIFICATION OF AYRE'S T-PIECE

as used by leading children's hospitals

This Infant's Set can be used either as an Anaesthesia Unit, or for Infant Resuscitation. There are no valves to go wrong, or cause added resistance. Dead space has been cut to an absolute minimum. Only seconds required to change from Mask to Intubation Setup.

Standard 15mm and 7/8" Mask Tapers



TO RECEIVE THE FOLLOWING LIST — QUOTE NUMBER 330-15 HFSC

1 of 330ES .75 lt. R/B Bag c/w End Plug
1 of 330-15L 15mm Bag Mount
1 of 330-15D Corrugated tube 11" long c/w 15mm mounts
1 of 330-15S 15mm Catheter Mount c/w fresh gas inlet
1 of 3301 Fresh Gas Feed Tube
1 of 620-15 Magill Oral 15mm Connector Size 4.0
1 of 7001M Lightweight Facepiece Angle
1 of 332E Rendell-Baker-Soucek Mask Size 1

RECOMMENDED BUT NOT INCLUDED

6 (1 each) 330CF Foregger Coles Tubes 8 to 18 F.G.
1 No. 332F Rendell-Baker-Soucek Mask Size 2
1 No. 332L Rendell-Baker-Soucek Mask Size 3
1 330LC Leather Case
1 of 330-15D Corrugated tube c/w 15mm mounts.

We recommend you purchase a 330LC Leather Case to store this equipment — prevents loss or damage.

MIE

MEDICAL & INDUSTRIAL EQUIPMENT
A division of Claudius Ash Incorporated
655 - 73rd Street, Niagara Falls, New York 14304

SEND FOR COMPLETE LITERATURE

PRECISE, ECONOMICAL, SAFE...

RALS POWER UNIT

...INSTANT ATOMIZATION FOR FAST TOPICAL ANESTHESIA

Fast, measured topical anesthesia is ready at your finger tips in a Rals Power Unit. Forget about pumping bulbs, uneven atomization, and limited spraying duration. The Rals Power Unit uses a non-toxic propellant, dichlorodifluoromethane (freon) to activate standard DeVilbiss Atomizers No's. 151, 152 and 163. Instantly, a fine mistlike spray is produced. A graduated solution vial is available for measuring the amount of solution administered.

The Rals Power Unit has been proven effective in cocainization prior to endotracheal intubation, endoscopic instrumentation, laryngotracheal insufflation, and in a variety of nose and throat procedures.

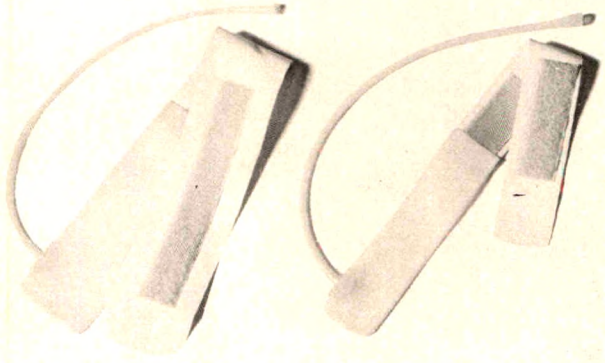
Rals Power Unit #168 are supplied six to a box with adaptor top and metal base. Illustration shows #152 atomizer. All styles in stock.

WRITE OR PHONE FOR LITERATURE, PRICE LIST.

RALS LABORATORIES DIVISION
SCHUEMANN Laboratories, Inc.
480 WEST AURORA ROAD • NORTHFIELD, OHIO 44067

SL-45

The tender touch

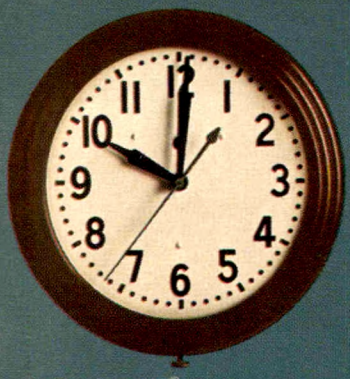


These soft, pliable blood pressure cuffs are ideal for use on newborns and infants. Incorporating a Latex bladder, minimizing any chances for skin irritation, and Silicon wrap-around with 12-inch inflating tube. They are secured by the Velcro hook and pile method, with no eyes to hook nor ends to tuck in. They are instantly peeled apart for easy removal.

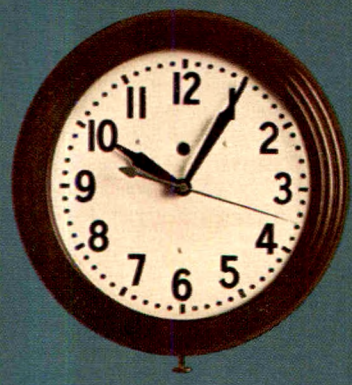
Cuffs are available in two sizes:
22080 - 1⅜ x 5" (new born)
22081 - 2¼ x 6" (infant)

For additional information write for brochure number 27.

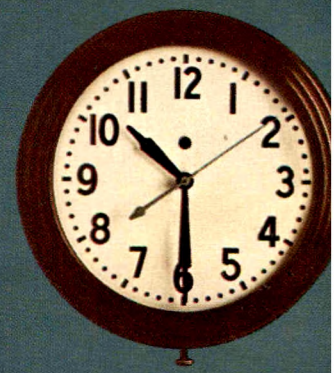
DUPACO
INCORPORATED
P.O. Box 98,
San Marcos, CA 92069



SUBLIMAZE® (fentanyl) has a uniquely short duration of analgesic action—for more precise control and minimal risk of prolonged narcotic effects.

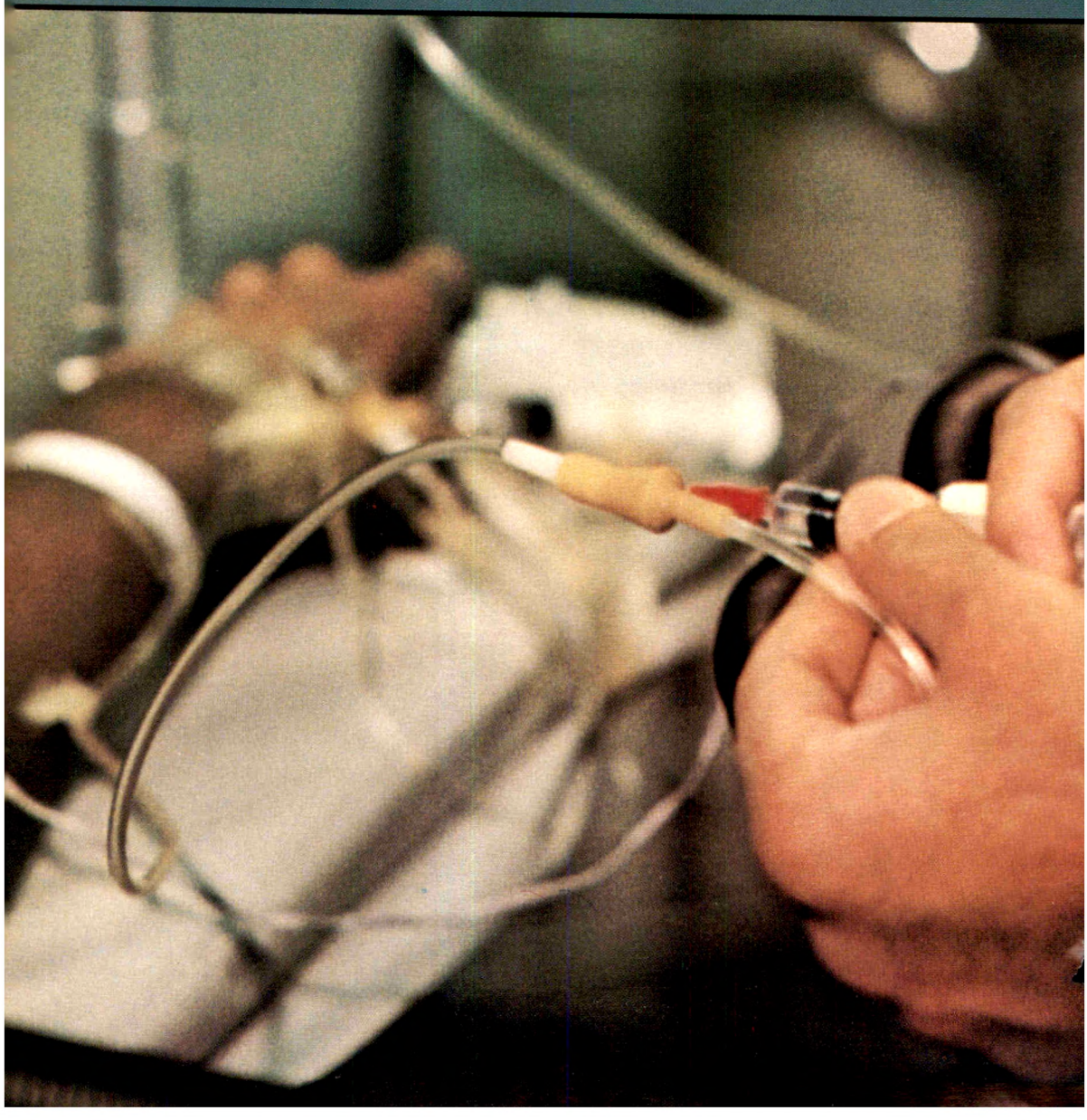


Within 5 minutes I.V., SUBLIMAZE® (fentanyl) reaches its peak analgesic effect.



Within 30 to 60 minutes I.V., the analgesic effect of SUBLIMAZE® (fentanyl) is almost completely dissipated.†

† Respiratory depressant effects may last longer than the analgesia and are increased and prolonged with large doses, multiple doses or use of postoperative narcotic analgesics.



For potent narcotic analgesic action with rapid onset and short duration:

SUBLIMAZE fentanyl provides profound analgesia without hypnosis and with little or no sedation. With this analgesia as a foundation, it is possible to use light general anesthesia in most cases.

SUBLIMAZE fentanyl is particularly suited for maintenance of analgesia after INNOVAR® injection* has been used for induction. It may also be used preoperatively, during surgery with any common general or regional anesthetic agent, and in the immediate postoperative period whenever the need for potent analgesic action arises.

SUBLIMAZE fentanyl is available both alone and as a component of INNOVAR injection.*

*INNOVAR injection is composed of a 50:1 mixture of droperidol 2.5 mg./cc. and fentanyl 0.05 mg./cc., with lactic acid for adjustment of pH to 3.5 ± 0.3.

SUBLIMAZE® (fentanyl) offers:

☐ Almost immediate analgesia—peak effect within 5 minutes I.V., 8 minutes I.M.

☐ Short duration of analgesic action—30 to 60 minutes with a single I.V. dose of up to 0.1 mg. (Respiratory depressant effects may last longer than the analgesia and are increased and prolonged with larger doses, multiple doses or use of postoperative narcotic analgesics.)

☐ No evidence of liver, heart, or kidney toxicity—expecially valuable in poor-risk patients. However, the drug should be administered cautiously in the presence of liver or kidney dysfunction or cardiac arrhythmias, and the dose should be appropriately reduced in poor-risk patients.

☐ Immediate reversibility by narcotic antagonists.

☐ Little or no histamine release—decreasing the risk of cardiovascular instability.

☐ Minimal emetic effect—has been used successfully to prepare nonfasting patients for awake intubation.

☐ Prevention or reversal of emergence delirium and tachypnea.

SUBLIMAZE® (fentanyl) injection

0.05 mg./cc. as the citrate.
Warning: May be habit forming.
Sodium hydroxide for adjustment of pH to 4.0—7.5

INNOVAR® injection and SUBLIMAZE® (fentanyl) injection are available for use only upon direction of a physician.
For information relating to Contraindications, Warnings, Precautions and Adverse Reactions for SUBLIMAZE fentanyl, please turn page.

© McNeil Laboratories, Inc., 1974

SUBLIMAZE® (fentanyl) injection

Description
Each cc. contains:
Fentanyl as the citrate . . . . . 0.05 mg.
Warning—May be habit forming.
Sodium hydroxide for adjustment of pH to 4.0–7.5
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY.

Actions SUBLIMAZE fentanyl is a narcotic analgesic with actions qualitatively similar to those of morphine and meperidine. SUBLIMAZE fentanyl in a dose of 0.1 mg. (2.0 cc.) is approximately equivalent in analgesic activity to 10 mg. of morphine or 75 mg. of meperidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. SUBLIMAZE fentanyl appears to have less emetic activity than other narcotic analgesics. Histamine assays and skin wheal testing in man, as well as *in vivo* testing in dogs, indicate that histamine release rarely occurs with SUBLIMAZE fentanyl.

SUBLIMAZE fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. It may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia, and bronchoconstriction.

The onset of action of SUBLIMAZE fentanyl is almost immediate when the drug is given intravenously; however, maximal analgesic and respiratory depressant effect may not be noted for several minutes. The average duration of action of the analgesic effect is 30 to 60 minutes. Following intramuscular administration, the onset of action is from seven to eight minutes, and the duration of action is from one to two hours.

Although the duration of the respiratory depressant effect is unknown, as with other narcotic analgesics it may be considerably longer than the analgesic effect.

Indications SUBLIMAZE fentanyl is indicated:
—for analgesic action of short duration during the anesthetic periods, premedication, induction, and maintenance, and in the immediate postoperative period (recovery room) as the need arises.
—for use as a narcotic analgesic supplement in general or regional anesthesia.
—for administration with a neuroleptic such as INAPSINE® (droperidol) injection as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.

Contraindications SUBLIMAZE fentanyl is contraindicated in patients who are hypersensitive to the drug.

Warnings PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* FENTANYL SHOULD HAVE APPROPRIATE SURVEILLANCE.

RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

If SUBLIMAZE fentanyl is administered with a tranquilizer such as INAPSINE droperidol, the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE fentanyl persists longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as 1/4 to 1/3 those usually recommended. A neuromuscular blocking agent compatible with the patient's condition may be required to control muscle rigidity which may develop with the use of SUBLIMAZE fentanyl.

Drug Dependence: SUBLIMAZE fentanyl can produce drug dependence of the morphine type and therefore has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE fentanyl in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure: SUBLIMAZE fentanyl should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition, SUBLIMAZE fentanyl may obscure the clinical course of patients with head injury.

Usage in Children: The safety of SUBLIMAZE fentanyl in children younger than two years of age has not been established.

Usage in Pregnancy: The safe use of SUBLIMAZE fentanyl has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

Precautions *The initial dose of SUBLIMAZE fentanyl should be appropriately reduced in elderly, debilitated and other poor risk patients. The effect of the initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms (see Actions) SUBLIMAZE fentanyl can also alter respiration. When SUBLIMAZE fentanyl is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia. When used with a tranquilizer such as INAPSINE droperidol, blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE fentanyl should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Postoperatively, respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists (levallorphan, nalorphine, and naloxone; consult individual prescribing information before using). Should respiration be compromised by muscle rigidity, assisted or controlled respiration and possibly a neuromuscular blocking agent will be required. The occurrence of muscle rigidity is related to the speed of intravenous injection and the incidence can be reduced by slow intravenous injection.

When a tranquilizer such as INAPSINE droperidol is used with SUBLIMAZE fentanyl, pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE fentanyl. When patients have received such drugs, the dose of SUBLIMAZE fentanyl required will be less than usual. Likewise, following administration of SUBLIMAZE fentanyl the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE fentanyl should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE fentanyl may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE fentanyl should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE fentanyl is used with a tranquilizer such as INAPSINE droperidol, hypotension can occur. If this occurs the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of INAPSINE droperidol, epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE droperidol.

Adverse Reactions As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE fentanyl are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur.

Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm and diaphoresis.

When a tranquilizer such as INAPSINE droperidol is used with SUBLIMAZE fentanyl, the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with antiparkinson agents. Postoperative drowsiness is also frequently reported following the use of INAPSINE droperidol.

Overdosage ***Manifestations:*** The manifestations of SUBLIMAZE fentanyl overdosage are an extension of its pharmacologic actions.
Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan, or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. Consult the package insert for the individual narcotic antagonists for details about use.

How Supplied SUBLIMAZE® (fentanyl) injection is supplied in 2 cc. (**NDC** 0045-0180-03) and 5 cc. (**NDC** 0045-0180-05) ampuls, in packages of 12.

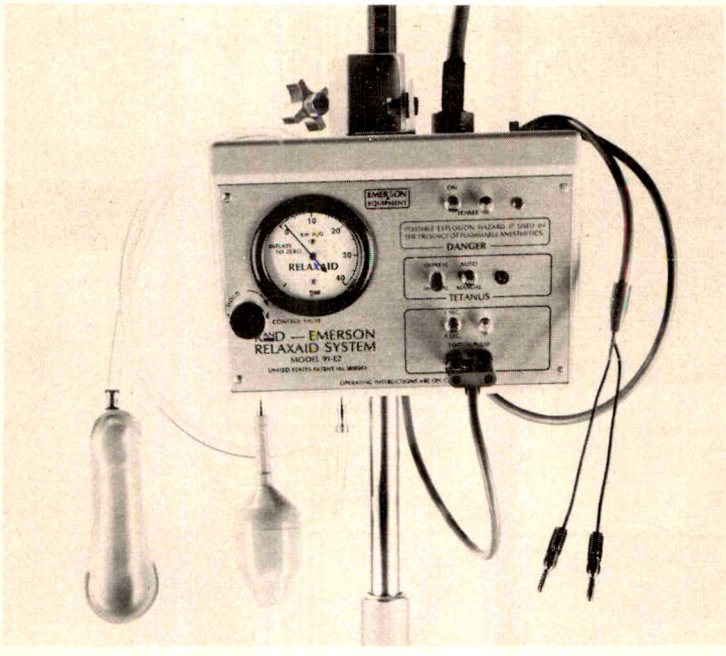
IMPORTANT: Complete dosage information is available in insert which accompanies each package (or on request). The drug is available only upon direction of a physician.

U.S. Patent No. 3,164,600

9/7

McNEIL McNeil Laboratories, Inc.
Fort Washington, Pa. 19034

R AND D-EMERSON RELAXAID ™



for CORRECT RELAXANT DOSAGE—
AVOIDANCE OF OVERDOSE—
PROMPT RECOVERY—

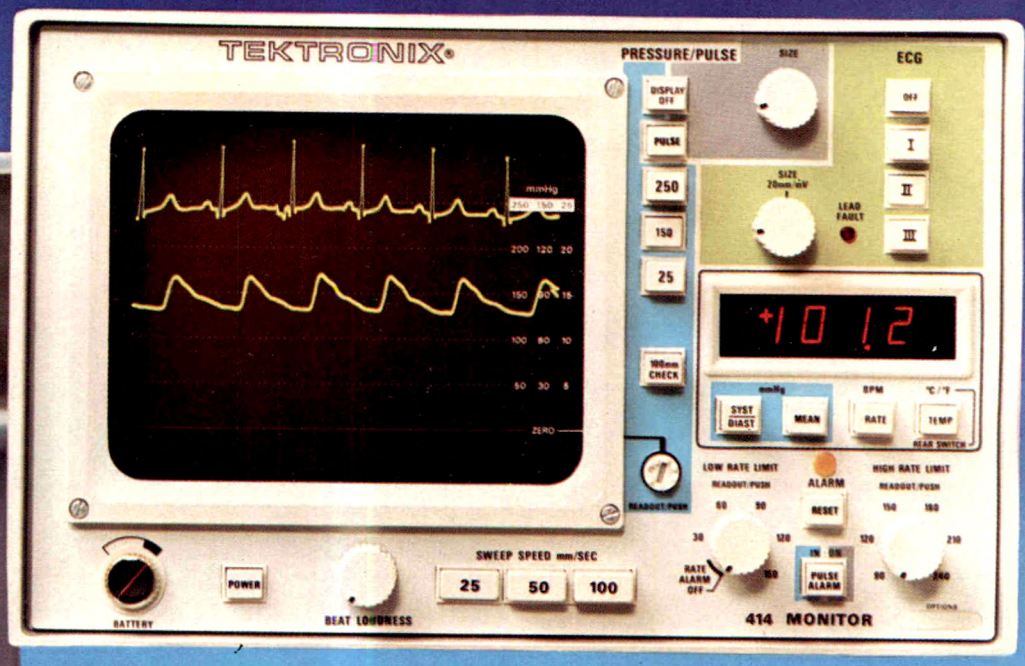
The stimulator is programed to deliver pulses, through electrodes, to the ulnar nerve. A flexible pneumatic bulb is placed in the patient's hand, with his fingers held against it by tape. The bulb is then air-filled to a pressure of 20 cm. H_2O. As the fingers flex, even slightly, compression of the bulb is registered on an aneroid gauge. The pattern of these responses keeps the anesthetist informed of the relaxant's effectiveness.

The more precise monitoring provided by the RELAXAID™ enables relaxant levels to be kept adequate but without overdose. During recovery the RELAXAID™ shows the return of strength to the patient's muscles.

Please request Form 91-E2

J. H. EMERSON COMPANY
CAMBRIDGE, MASSACHUSETTS 02140

Introducing the most complete monitor capability in a single compact instrument.



NEW Tektronix 414 Portable Patient Monitor

ECG. Temperature. Arterial, venous or pulmonary wedge pressure. Peripheral pulse. Only Tektronix 414 offers every feature for monitoring these vital signs—all neatly packaged in a single, portable unit. For increased accuracy and convenience, the 414 gives digital readout of heart rate, systolic/diastolic blood pressures, mean blood pressure, or temperature. Rate alarm limits are also set digitally.

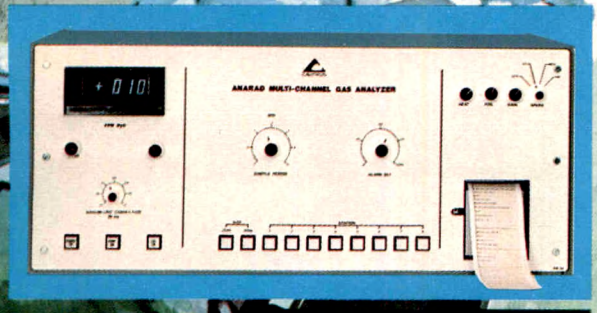
And because the 414 permits cordless (battery) operation, it can be as easily used for cardiac catheterization as for surgery and recovery. Weight of a fully equipped 414 is approximately 12 lbs.

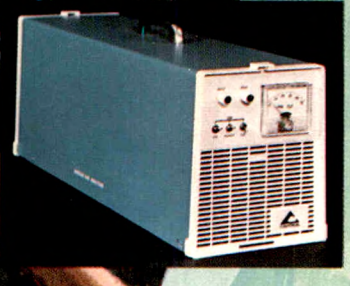
For more information or a demonstration of any of Tektronix Portable Patient Monitors in your facility, please write to Tektronix, Inc., P.O. Box 500, Beaverton, Oregon 97077. *Or call collect:* (503) 644-0161, extension 6510.

Excellence in Patient Monitoring

TEKTRONIX®
committed to technical excellence

Is This Area Safe for You to Work in?





CAVITRON™ Operating Room Environmental Monitors

Central Station Model EM-30

This multi-channel Gas Analyzer establishes a monitoring capability for up to eight individual operating rooms. Samples are drawn from each room automatically, cycled analysis performed, and barometrically corrected. Results displayed at the O.R. control station.

Portable Model EM-10

The compact EM-10 is a valuable adjunct to Cavitron's Central Station. It provides bio-engineering personnel with a facility to respond quickly to areas of pollution and to establish the source of contamination.

Our solid-state detection units provide the finest in environmental monitoring techniques, with permanent documentation on a continuous time basis.

Distributed By

CAVITRON/KDC MEDICAL SALES
Division of Cavitron Corporation
Headquarters: 1528 West Embassy Street
Anaheim, California 92802 • 714/776-1811
Eastern Office: 615 Winters Avenue,
Paramus, New Jersey 07652 • 201/265-8393

51ST CONGRESS

MARCH 6-10, 1977

International Anesthesia Research Society

DIPLOMAT RESORT AND COUNTRY CLUBS
HOLLYWOOD, FLORIDA

CALL FOR PAPERS

August 2, 1976—Deadline for submission of titles and abstracts. Application forms are available from: John T. Martin, M.D., Chairman, Program Committee, Medical College of Ohio at Toledo, P.O. Box 6190, Toledo, Ohio 43614.

Outpatient Evaluation: A New Role for the Anesthesiologist

ELIZABETH A. M. FROST, MD*

Anesthesiology, although still a relatively young specialty, is expanding beyond the operating room. The author reports material savings in many areas through presurgical interviews in the outpatient department by anesthesiologists.

IN JULY 1972, in an attempt to reduce hospital stay and cost,[1-3] the Ambulatory Care Service of the Bronx Municipal Hospital Center and the Department of Anesthesiology[4,5] initiated a preadmission evaluation clinic, a project proposed as long ago as 1949.[6]

The present article describes our experiences and impressions gained in such a clinic over the past 3 years and the impact of our program on patient care and bed utilization. The clinic has now been established as a permanent part of the Outpatient Department.

METHODS AND MATERIALS

The Bronx Municipal Hospital Center is a 990-bed hospital servicing a large urban community. In 1973 and again in 1974 there were approximately 23,000 admissions, of which 65% were emergency. Of 8000 surgical operations performed, 70% were elective. The program was initially confined only to the general surgical and the gynecologic departments. Later, we expanded the facility to accommodate all services.

Patients are seen first by a surgeon in the surgical outpatient clinic and are referred to the preadmission screening clinic when scheduled for elective surgery. Referral is in no way dependent on the magnitude of the planned surgical procedure, as we have even screened patients for aortic aneurysm resection.

The referring surgeon completes a check form (figure), specifying dates of admission and operation and any special preoperative studies to be made on an outpatient basis. Urinalysis, complete blood count, SMA6 blood typing, and serum electrolytes are ordered for all surgical admissions. Chest x-ray and ECGs are ordered for patients over the age of 30 or if indicated by past medical history. These studies may also be ordered on a "STAT" basis at the discretion of the anesthesiologist at the time of interview. Papanicolaou smears are taken on all adult women patients. All test requests are stamped PRE-OP ADM to identify the source of the specimen and to promote prompt return of results. With the exception of special x-ray studies, the results of which are entered on the chart prior to admission, all other results are returned to the preadmission clinic by 1330 hr, by which time all old records on the patients have also been obtained.

A coordinating clerk in the Ambulatory Care Service schedules a clinic appointment within 10 days of the planned admission. Special radiologic procedures, such as barium studies, are scheduled for the same day. Patients are given an instruction sheet printed in both English and Spanish. They are asked to report, fasting, to the coordinating clerk's office in the hospital at 0830 hr on the day of the preadmission interview.

When patients report back to the clinic,

*Assistant Professor, Department of Anesthesiology, Albert Einstein College of Medicine, Bronx, New York 10461.

Paper received: 5/27/75
Accepted for publication: 10/3/75

BRONX MUNICIPAL HOSPITAL CENTER

Pre-Admission Request Sheet

DATE: MARCH 3, 1975

NAME: LOUIS D. AGE: 36

CHART NO. 666799

ADDRESS: 11-20 WILLIAMSBRIDGE ROAD BRONX, NEW YORK

HOME TELEPHONE NO. 633-5040

Referring Clinic GENERAL SURGERY Referring M.D. DR. ALAN DONALD Ext.: 432

Diagnosis INGUINAL HERNIA Procedure to be performed LT. HERNIORRPAPHY Donors 1

Preferred within 7 days/weeks from today. Type of anesthesia: General √ or Local ____

Admission to ward: 6 S day before or day of procedure (circle one).

Scheduled date of admission: MARCH 9, 1975 Scheduled date of operation: MARCH 10, 1975

The following examinations/tests are needed (check only those required):

O = Ordered D = Done R-nl = Results normal R-abnl = Results abnormal

A. LABORATORY	O	D	R-nl	R-abnl
1. Urinalysis routine	√	√	√	
2. CBC	√	√	√	
3. SMA 6	√	√	√	
4. Blood Type & RH	√	√		
5. SMA 12				
6. VDRL				
7. Pap Smear				
8. Chest X-ray	√	√	√	
9. EGG	√	√	√	
10. Urine C & S	√	√	√	
11. Other_____				

B. CONSULTATIONS	O	D	R-nl	R-abnl
1. Medical				
2. Anesth.	√	√	√	
3. Other_____				
C. SPECIAL TESTS				
1. Sigmoidoscopy				
2. Cystometrics				
3. IVP				
4. Barium Enema				
5. UGI Series				
6. GB Series				
7. Hysterosalpingogram				
8. Chain Cysto-urethrogram				
9. Other_____				

D. FINAL CLEARANCE FOR SURGERY: YES ☑ NO ☐

1. If no, patient notified yes ☐ no ☐
2. If no, referring M.D. notified yes ☐ no ☐
3. If no, Admitting Office notified yes ☐ no ☐

Medicare √ Medicaid_____ Other Insurance _____

Self Pay (Fee) $_____

DATE OF SCREENING W/U 3/6/75

RC 7/73

FIGURE. Check list completed for all patients attending the pre-admission screening clinic.

they are interviewed by an anesthesiologist, who reviews the current laboratory results and past history, and the check-list begun by the surgeon is completed. An internist is always present for consultation. Should any anesthetic or medical contraindication to the proposed surgical procedure be found, the patient is directed immediately to the appropriate specialty clinic and the admission is postponed. Under these circumstances, the referring surgeon, the admitting office, the operating room, and the patient are mutually informed.

For an occasional patient—as one with a recently developed upper respiratory-tract infection or even one with unexpected social obligations—we delay admission for a few days and inform those concerned. Should no contraindication to the proposed procedure be found, a final clearance check is made by the anesthesiologist on the master sheet and the patient directed back to the admitting office for final instructions. No patient leaves the clinic until final disposition has been made. We evaluate all patients, including those scheduled by the surgeon for local anesthesia; thus we are conversant with all elective procedures scheduled.

RESULTS

The system has now been operative for over 3 years, during which time we have

TABLE 1
Source of Referrals of ± 3500 Patients

Clinic	Percentage
Gynecology	45
General surgery	25
Ophthalmology	9
Urology	8
Otolaryngology	8
Orthopedic	5

seen over 3500 patients (table 1). Scheduled admission has consistently had to be withheld in about 6% of patients—most commonly because of unsuspected or uncontrolled diabetes, upper respiratory infections, severe hypertension, anemia, and pregnancy. Of these, some 17% have been cleared later the same day after repeating laboratory work, respiratory function tests, or comparing x-rays or ECGs. Nurse technicians give intensive instruction when needed to the diabetic or hypertensive patient; thus operations are often rescheduled within a week, rather than after the enormous loss of time resulting when a patient is shuffled back through normal outpatient channels.

Both preoperative and total hospital stay have been significantly reduced in comparison with data obtained from a similar group of surgical patients before establishment of the clinic.

Comparison of 89 patients over a 3-month period in 1973 with 90 nonclinic patients who had the same procedure during the same period in 1972 showed a patient-day reduction of 348 days, or an average of 3.91 days per patient (table 2).

DISCUSSION

In the relative safety of an outpatient department, where patients still maintain their identities, we have found ourselves bombarded by questions about the anesthetic technic. Much of the time of the interview is spent in allaying fears of anesthesia engendered by such ambiguous journalistic reports as the "truth serum" myth. We have found the clinic an ideal setting for explaining block and regional technics, for telling patients whether the results of their tests are normal, and whether they are in optimal physical shape for the proposed surgical procedure. When any abnormalities are revealed, the problem is always taken care of promptly.

As the clinic is directed by anesthesia staff from the recovery room and respiratory care units, continuity of anesthetic care is possible from outpatient evaluation to postanesthetic management. The availability of all laboratory reports and previous records as well as close interdepartmental cooperation have all contributed to greatly improved preoperative assessment. No more are junior house staff members required to make major preoperative decisions on evening rounds. When patients become better informed, they become lesser anesthetic risks.

Even if the surgical service has no available beds, the clinic patients are treated as semiemergency admissions and are admitted at the prearranged time to an empty bed elsewhere in the hospital. To avoid cancellation in the operating room because of overscheduling, our patients are first on the day's list. As our blood bank depends on voluntarily donated blood, the clinic provides a convenient place to explain to patients the need to find donors and the advantages to them of this system. Bed utilization has been improved by having faster turnover on surgical and gynecologic services and by increasing the census in areas not usually filled to capacity.

TABLE 2
Comparison of Patient Days, 1972 and 1973 (3-month period)

Operation	(Number of cases)	1972 (before system) Preoperative days	1972 (before system) Total days	1973 (after system) Preoperative days	1973 (after system) Total days	Days saved Preoperative days	Days saved Total days
Bilateral tubal ligation	(36)	1.97	7.63	(39) 1.33	5.26	1.64	2.37
Total abdominal hysterectomy	(33)	4.82	13.21	(23) 2.0	8.17	2.82	7.04
Breast mass excision	(21)	2.81	6.62	(27) 1.48	3.15	1.33	3.47

Comparison of patients in these 3 operative groups shows similar savings in preoperative hospital days for the extended periods. Postoperative hospital days showed a relatively comparable reduction after establishment of the clinic.

The nonhospital benefits to patients are the morning timing, which allows parents to see children off to school. The midday break also permits them to return home if necessary. Flexibility of admission combined with direct patient contact makes it possible to change an admitting date because of social pressures without losing the chance altogether for the operation. Employees are given a more exact idea of how long they can expect to be off the job.

Operating-room utilization has similarly been improved. Prior to the system, if a case were canceled after 1900 hr the previous evening, rarely could another case be prepared to fill the slot; thus the room lay fallow. Now that approximately 40% of scheduled surgical cases are being evaluated through the system, the operating-room cancellation rate has been markedly reduced.

Perhaps the biggest problem of the program is the question of reimbursement to the hospital and to the physicians involved. At present, Medicare, Medicaid, and other insurance carriers pay the Health and Hospital Corporation about $205 per inpatient hospital day at the Hospital Center. The same insurance carriers allow only $41 for outpatient presurgical evaluation at our clinic. No allowance is made for outpatient anesthesiology consultation.

Clearly, the system has become extremely costly to the hospital and physicians under present legislation. The exact cost involved is currently under review. With the passage of Public Law 92-603, preadmission evaluation for certain groups of patients will become mandatory. Insurance carriers are asking for justification of inhospital patient days. To make such programs as ours attractive to everyone, reimbursement to hospitals and physicians must become more reasonable than the present schemes allow.

We do feel, however, that the main advantages have come in improved patient care. The anesthesiologist is rightfully and legally the only physician who can fully assess a patient as an anesthetic risk. To be able to do this when time is still available to correct problems without costing the patient undue anxiety, time, or money is ideal.

No complications attributable to the clinic have occurred, and strangely enough, none of our patients have changed their minds about the procedure during the testing. Only one of our patients out of 3500 developed a ventricular arrhythmia immediately before induction and was a last-minute cancellation on the surgical schedule. In the near future, we hope that the clinic will become an integral part of an outpatient surgical unit, currently under development.

Anesthesiology, although still a relatively young specialty, is expanding rapidly out of the operating room. It is our experience that the preadmission clinic provides a natural, satisfying, and vitally important place for the modern anesthesiologist.

ACKNOWLEDGMENT

I would like to thank Dr. Richard Collens and the Ambulatory Care Service of the Bronx Municipal Hospital Center for invaluable help in the inauguration and early running of this program.

REFERENCES

1. Freilich H: Preoperative laboratory testing in out-patient department shortens hospital stay. NY State J Med 65:2163-2166, 1965

2. Janis M, Downs JB: The anesthesia screening clinic. JAMA 223:692, 1973

3. Anderton JM: The value of joint anaesthetic and surgical pre-operative assessment. Br J Anaesth 44:183-189, 1972

4. Loder RE, Richardson HJ: Pre-operative anesthetic out-patient clinic. Lancet 1:1177-1178, 1954

5. Green RA, Howalt DDC: An anaesthetic out-patient clinic. Anaesthesia 7:40-45, 1952

6. Lee JA: The anaesthetic out-patient clinic. Anaesthesia 4:169-174, 1949

Arterial Hypoxemia Caused by Intravenous Ketamine

E. K. ZSIGMOND, MD*
A. MATSUKI, MD†
S. P. KOTHARY, MBBS‡
M. JALLAD, BS§

Ketamine given IV in a dose of 2 mg/kg caused a significant reduction in Pa_{O_2} in 7 patients spontaneously breathing with an unassisted airway. Under the same conditions, in 7 patients, ketamine (2 mg/kg IV) preceded by diazepam (0.2 mg/kg IV) also caused a reduction in Pa_{O_2} not significantly different from that caused by ketamine. In some patients, alarmingly low levels of Pa_{O_2} ($\leq$ 40 torr) were seen following ketamine administration. Based on these findings, the authors recommend that O_2 and ventilatory assistance accompany ketamine given IV for anesthesia.

SINCE its introduction into clinical anesthesia,[1,2] ketamine has geen given IV for induction and maintenance of general anesthesia without respiratory assistance and O_2 administration, in the belief that it causes neither respiratory depression nor airway obstruction from jaw relaxation.[3-5] Ketamine was even recommended as an anesthetic induction agent for patients with bronchial asthma.[6] However, no blood-gas studies or determinations of the response to CO_2 inhalation were reported to substantiate these claims.

The present study was therefore undertaken to evaluate arterial blood gases after ketamine administration.

MATERIALS AND METHODS

Patient Material.—Fourteen adult gynecology patients (ASA physical states I-II) were selected for the study. Patients gave informed consent to arterial catheterization and blood sampling. No patients were receiving any medications at the time of the study and none was pregnant. No significant differences in age, weight, or other physical characteristics were observed between the 2 groups studied. Group I (N=7) received 2 mg/kg of ketamine IV over 30 seconds; group II was given the same dose of ketamine preceded by 0.2 mg/kg of IV diazepam.

Experimental Method.—All patients received routine preoperative medication consisting of 0.15 mg/kg of diazepam and 0.007 mg/kg of atropine IM, combined with either 1.5 mg/kg of meperidine (N=4) or 0.15 mg/kg of morphine (N=8). One patient received 0.75 mg/kg of promethazine HCl with 0.75 mg/kg of meperidine and 0.008 mg/kg of atropine IM, and another patient, 0.036 mg/kg of droperidol with 0.7 μg/kg of fentanyl and 0.007 mg/kg of atropine IM.

On the patient's admission to the anesthesia study unit, a 16-gauge Teflon catheter was inserted into an antecubital vein

*Professor of Anesthesiology, Department of Anesthesiology, University of Michigan Medical Center, Ann Arbor, Michigan 48104.

†Assistant Professor of Anesthesiology, Department of Anesthesiology and Anesthesia Research Laboratories, University of Hirosaki, Hirosaki, Aomori-Ken, Japan.

‡Research Associate, Departments of Anesthesiology and Anesthesia Research Laboratories, University of Michigan Medical Center.

§Anesthesiology Technician, Departments of Anesthesiology and Anesthesia Research Laboratories, University of Michigan Medical Center.

Paper received: 4/22/74
Accepted for publication: 9/8/75

and 5% dextrose in 0.2% NaCl solution was started to keep the IV path open for drug injections. A 20-gauge Riley needle was inserted into the contralateral brachial artery, and a 20-minute rest period was allowed before the baseline sampling for blood gases. In the ketamine group, 2 mg/kg of ketamine was injected IV in 50 ml IV solution over 30 seconds, and blood-gas samples were taken before and at 2, 5, and 10 minutes after injection.

In the diazepam-ketamine group, first diazepam (0.2 mg/kg) was given in 30 ml of IV fluid over 30 seconds and, after 5 minutes, 2 mg/kg of ketamine was given over 30 seconds with 50 ml of IV solution. Blood-gas samples were obtained before diazepam and at 2, 5, and 10 minutes after ketamine administration. No airway support, ventilation, or O_2 were given, with the exception of 1 patient of the ketamine group who became cyanotic after the 2-minute sample was taken.

Positional changes, skin disinfection, and stimulation were avoided during the study. No additional doses of ketamine or any other IV or inhalational anesthetic agents were given, even if the patient fully awakened from sleep during the 10-minute period after ketamine administration. Additional doses of ketamine or thiamylal and muscle relaxants for endotracheal intubation were used only after the completion of blood sampling.

Laboratory Analysis.—All heparinized blood samples were immediately studied by the Radiometer Copenhagen Astrup Blood Gas Analyzer for Pao_2, $Paco_2$, and pH. Duplicate determinations were carried out on samples with a low Pao_2 by a similar analyzer, and the low Pao_2 values were found to be accurate within 5%.

Monitoring.—ECG, pulse, and blood pressure were continuously monitored throughout the study. With the exception of 1 patient in the ketamine group, chest plethysmographic recordings were also continuously taken.

RESULTS

A significant reduction in the mean Pao_2 ($p<0.01$) and elevation in the mean $Paco_2$ ($p<0.01$) occurred 2 minutes after ketamine injection (table 1). Arterial hypoxemia persisted throughout the study, and both Pao_2 and $Paco_2$ remained abnormal

TABLE 1
Blood-Gas Changes in Patients Induced with Ketamine and Diazepam-Ketamine Combination

Patient groups	N	Before drug administration			After drug administration									
					2 minutes			5 minutes			10 minutes			
		pH, units	Pao_2, torr	$Paco_2$, torr	pH, units	Pao_2, torr	$Paco_2$, torr	pH, units	Pao_2, torr	$Paco_2$, torr	pH, units	Pao_2, torr	$Paco_2$, torr
Ketamine 2 mg/kg IV	7	7.40 ±0.02*	84.0 ±3.4	34.0 ±1.5	7.37 ±0.02	58.0† ±6.5	38.0† ±1.1	7.37 ±0.02	67.2‡ ±5.1	39.0† ±1.3	7.36 ±0.02	74.8‡ ±3.8	38.4‡ ±1.6
Ranges of values		(7.35-7.5)	(72-96)	(25-37)	(7.32-7.44)	(35-84)	(35-43)	(7.32-7.44)	(45-76)	(33-43)	(7.32-7.47)	(65-92)	(33-46)
Diazepam 0.2 mg/kg and ketamine 2 mg/kg IV	7	7.38 ±0.01	74.4 ±7.0	37.0 ±1.7	7.34 ±0.01	46.6† ±3.8	43.7‡ ±1.2	7.34 ±0.02	55.0‡ ±3.0	43.3† ±1.6	7.35 ±0.02	65.5‡ ±4.0	42.2‡ ±1.0
Ranges of values		(7.35-7.44)	(57-102)	(34-46)	(7.3-7.4)	(31-59)	(40-47)	(7.3-7.43)	(46-71)	(37-48)	(7.3-7.42)	(54-85)	(39-47)

*Standard error of the mean.
†Significant change from baseline values at $p<0.01$.
‡Significant change from baseline values at $p<0.05$.

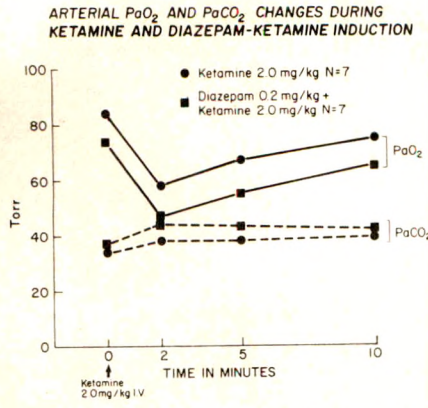


FIG. 1. Pao_2 and $Paco_2$ changes after ketamine and diazepam-ketamine administration.

even at 10 minutes after ketamine administration (fig 1). The changes from baseline values in mean Pao_2 and $Paco_2$ in the diazepam-ketamine group, with the exception of mean $Paco_2$ at 2 minutes ($p \leq 0.05$) were not significantly different from those observed in the ketamine group (table 1).

Diazepam neither antagonized nor potentiated the effect of ketamine on arterial blood gases. The changes in mean arterial pH were not statistically significant in either group. Some patients had an alarming decrease in Pao_2 (eg, from 96 to 35 torr and from 85 to 39 torr) and marked increases in $Paco_2$ (eg, from 34 to 44 torr and from 35 to 47 torr) (table 1).

A significant decrease in the respiratory rate occurred in both study groups at 3 minutes after ketamine injection (table 2). The ranges in respiratory rates in both groups indicate the varied respiratory response to ketamine. Although a few patients showed an increase in tidal volume, 50 to 60% of the patients developed apnea after ketamine injection. An example of the pattern is shown in figure 2. Pretreatment with diazepam did not alter the incidence or duration of apnea.

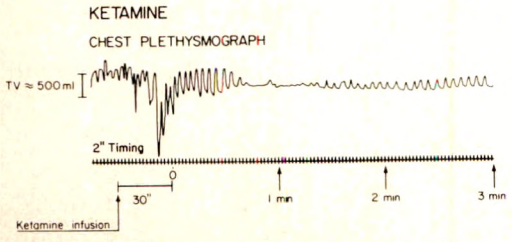


FIG 2. Typical chest-plethysmographic tracing from a patient after ketamine administration.

TABLE 2
Respiratory Rate Changes in Patients Induced with Ketamine and Diazepam-Ketamine Combination

Patient groups	N	Mean respiratory rates per minutes*					
		Before ketamine administration	After ketamine administration				
			1 minute	2 minutes	3 minutes	4 minutes	5 minutes
Ketamine 2 mg/kg IV	6	19.0 ± 3.92†	13.0 ± 4.17	11.0 ± 6.42	14.0 ± 2.61‡	17.0 ± 4.82	20.0 ± 5.23
Ranges of values		(15-24)	(7-18)	(0-20)	(11-18)	(10-21)	(12-24)
Diazepam 0.2 mg/kg IV and ketamine 2 mg/kg IV	7	19.0 ± 3.16	12.0 ± 5.97‡	12.0 ± 5.37‡	13.0 ± 2.55‡	14.0 ± 2.2‡	14.0 ± 2.08‡
Ranges of values		(15-24)	(3-20)	(5-18)	(8-16)	(11-16)	(12-16)§

*Respiratory rates derived from chest plethysmographic tracings.
†Standard deviation.
‡Significant change from baseline values at $p \leq 0.05$.
§N = 4.

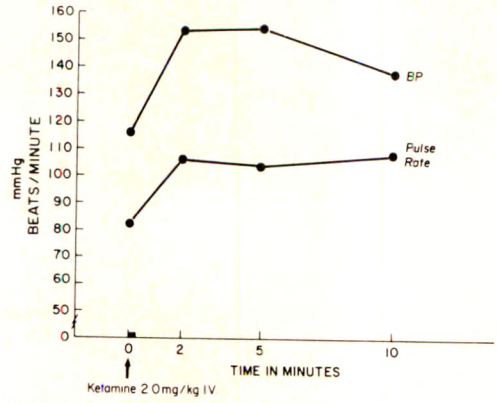


FIG 3. Blood pressure and pulse rate changes following IV ketamine administration.

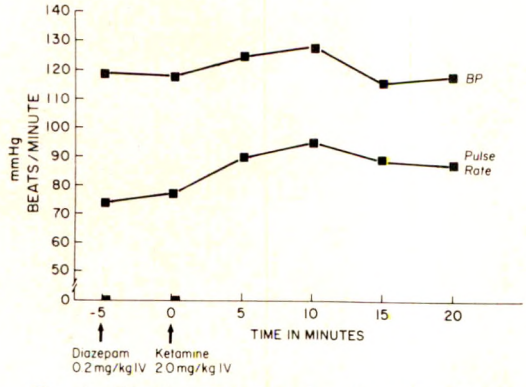


FIG 4. Blood pressure and pulse rate changes following diazepam-ketamine administration.

Arterial blood pressure and pulse rate were elevated in the ketamine group (fig 3). Diazepam reduced these effects of ketamine (fig 4). No arrhythmias or airway obstruction were observed in any patient. Analysis of circulatory effects will be presented in a later publication.

DISCUSSION

Despite reports on the lack of respiratory depressant effect of ketamine[7-9] and its recommendation as an induction agent for patients with airway and respiratory problems,[2,4,6] marked arterial hypoxemia was observed in our studies. The concomitant increase in $Paco_2$ makes it likely that ketamine directly depresses the respiratory center. Indeed, several patients became apneic for more than 30 seconds following ketamine administration.

Regardless of the exact mechanism of the arterial hypoxemia induced by ketamine, it must be promptly corrected, since it results in severe oxyhemoglobin desaturation (eg, 98 to 67% and 95 to 71%) in some patients. If this alarming result is allowed to persist, even briefly, in patients with anemia and/or with reduced cardiopulmonary reserve, it may result in morbidity or mortality.

Therefore, we recommend adequate ventilatory assistance and O_2 administration during induction of anesthesia either with ketamine or diazepam-ketamine combination. Arterial blood gases, catecholamines, O_2 uptake, and CO_2 response, especially in patients with abnormal cardiopulmonary reserve, should be studied further to elucidate the mechanism of arterial hypoxemia following ketamine administration in man.

ACKNOWLEDGMENT

We are grateful to all the patients who volunteered for the study and to Parke, Davis and Company for their financial support of our investigations. We are also indebted to the staff of the University of Michigan Medical Center Department of Gynecology and Obstetrics, who allowed us to study their patients.

REFERENCES

1. Domino EF, Chodoff P, Corssen G: Human pharmacology of CI-581, a new intravenous agent chemically related to phencyclidine. Fed Proc 24: 268, 1965

2. Corssen G, Domino EF: Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. Anesth & Analg 45:29-40, 1966

3. Corssen G: Clinical use of CI-581. Acta Anaesthesiol Scand 25:416-418, 1966

4. Corssen G: Recent developments in the anesthetic management of burned patients. J Trauma 7:152-156, 1966

5. Corssen G, Miyasaka M, Domino EF: Changing concepts in pain control during surgery: dissociative anesthesia with CI-581. A progress report. Anesth & Analg 47:746-759, 1968

6. Corssen G, Gutierrez J, Reves JG, et al: Ketamine in anesthetic management of asthmatic patients. Anesth & Analg 51:588-596, 1972

7. Wilson RD, Nichols RJ, McCoy NR: Dissociative anesthesia with CI-581 in burned children. Anesth & Analg 46:719-724, 1967

8. Wilson RD, Knapp C, Traber DL, et al: Safe management of child with a contracted neck: a new method. South Med J 63:1420-1425, 1970

9. Lorhan PH: Emergency anesthesia for aged. Int Anesthesiol Clin 9:29-51, 1971

Factors Affecting A-aDo_2 After Open-Heart Surgery

ATSUO SARI, MD*
YOSHIAKI OKUDA, MD†
HIROSHI TAKESHITA, MD‡
TATSUROH ODA, MD§
Ube, Yamaguchi, Japan‖

Intrapulmonary shunt, cardiac output, and O_2 consumption as factors contributing to alveolar-arterial O_2 tension difference (A-aDo_2) were tested in 11 patients after open-heart surgery. A-aDo_2 was well correlated with intrapulmonary shunt, as expected, but no correlation was found between cardiac index (CI) and intrapulmonary shunt. When total shunt (venous admixture) was above 11%, there was an inverse correlation between A-aDo_2 and CI, and it was observed that CI falling below 2.5 L/min/sq m contributed significantly to the enlargement of A-aDo_2. Low Pao_2 (<65 torr, breathing room air) was characterized by larger arterial-mixed venous O_2 content difference than high Pao_2 (>65 torr, on room air), indicating that A-aDo_2 was influenced by cardiac output relative to metabolic demand. Intrapulmonary shunt played a main role in increasing A-aDo_2 after open-heart surgery, and systemic factors, including changes in cardiac output and O_2 consumption, also contributed to development of hypoxia.

OUR previous investigation[1] demonstrated a gradual fall in arterial O_2 tension (Pao_2) following open-heart surgery and proposed criteria for postoperative respiratory management. Since Kelman and coworkers[2] proposed that decrease in cardiac output ($\dot{Q}t$) leads to hypoxia, several investigators[3-5] have directed their attention to $\dot{Q}t$ as a possible factor affecting postoperative arterial oxygenation, but have found no consistent relationship postoperatively between $\dot{Q}t$ and alveolar-arterial O_2 tension difference (A-aDo_2).

The present study examines possible relationships between increased A-aDo_2 and intrapulmonary shunt, $\dot{Q}t$, and O_2 consumption ($\dot{V}o_2$) in postoperative open-heart patients.

METHOD

The 11 patients studied represented 2 cases of atrial septal defect, 4 cases of ventricular septal defect, 4 cases of tetralogy of Fallot, and 1 case of mitral stenosis. Ages ranged from 5 to 21 (average 12) years (table 1). All survived except 1 tetralogy patient, who died of heart failure on the 41st postoperative day.

Anesthesia.—Premedication consisted of atropine sulfate (0.02 mg/kg, maximal dose 0.5 mg) and nitrazepam* (5 to 10 mg) in adults or pethidine (meperidine) (1 mg/kg) in children. Anesthesia was induced with thiopental sodium (5 mg/kg in adults

*A benzodiazepine derivative, not yet available commercially in the USA. Ed.

*Assistant Professor, Department of Anesthesiology.
†Associate Professor, Department of Anesthesiology.
‡Professor, Department of Anesthesiology.
§Instructor, Department of Surgery.
‖Yamaguchi University School of Medicine, Ube, Yamaguchi, Japan.

Paper received: 12/23/74
Accepted for publication: 11/11/75

TABLE 1
Patient Characteristics

Case	Age, yr	Sex	Diagnosis	MPAP, torr
1	14	F	VSD	27
2	5	F	VSD	10
3	10	F	ASD	17
4	5	F	ASD	33
5	20	M	MS	—
6	7	M	VSD	100
7	19	F	VSD	45
8	8	M	TOF	20
9	21	M	TOF	30
10	11	M	TOF	2
11	11	F	TOF	—

MPAP = mean pulmonary arterial pressure.
VSD = ventricular septal defect.
ASD = atrial septal defect.
MS = mitral stenosis.
TOF = tetralogy of Fallot.

or with halothane-N_2O in children. Intubation was facilitated by succinylcholine. Anesthesia was maintained with 0.5 to 1% halothane and N_2O-O_2 (2:2) in a semi-closed system. In all cases, a disposable-sheet bubble oxygenator with roller pump was used.

Measurements. — Teflon catheters were placed percutaneously in either a radial or brachial artery and in the superior vena cava. The venous catheter was moved into the pulmonary artery before chest closure. The catheters were used for arterial and mixed venous blood sampling, pressure monitoring, and $\dot{Q}t$ determination. The $\dot{Q}t$ was determined by the dye-dilution technic, with a single injection of indocyanine green. A densitometer† and a Harvard‡ infusion withdrawal pump were used.

Measurements were made at the end of operation and 4, 8, and 24 hours later, with patients breathing air or 100% O_2. Arterial and mixed venous P_{O_2}, P_{CO_2}, and pH were measured by IL meter§ at 37 C within 10 minutes of collection.

Calculations.—Total shunt (venous admixture $\dot{Q}_{VA}/\dot{Q}t$)[1] and true shunt ($\dot{Q}s/\dot{Q}t$), with patients breathing air and 100% O_2, respectively, has been widely used to detect the contribution of ventilation/perfusion inequalities to the $\dot{Q}_{VA}/\dot{Q}t$.[4-9] The $\dot{Q}_{VA}/\dot{Q}t$ consists of the anatomic shunt, atelectasis, ventilation/perfusion inequalities, and diffusion gradient. The $\dot{Q}s/\dot{Q}t$ represents the blood flow through anatomic shunt and atelectasis. The diffusion gradient across normal alveolar membranes is negligible at alveolar O_2 tension (P_{AO_2}) >100 torr.

O_2 content in arterial blood (Ca_{O_2}) and in mixed venous blood ($C\bar{v}_{O_2}$) was calculated from the following equation:

O_2 content = 1.39 × Hb × S_{O_2} + 0.0031 × P_{O_2}, where 0.0031 is the solubility coefficient for O_2 in blood at 37 C and S_{O_2} is O_2 saturation; read from a blood-gas calculator,[10] this was estimated to be 1 while 100% O_2 was breathed.

$\dot{Q}_{VA}/\dot{Q}t$ was calculated from the following equation:

$$\frac{\dot{Q}_{VA}}{\dot{Q}t} = \frac{C\acute{c}_{O_2} - Ca_{O_2}}{C\acute{c}_{O_2} - C\bar{v}_{O_2}}$$

where $C\acute{c}_{O_2}$ is end-pulmonary capillary O_2 content, and is calculated on the basis of the end-pulmonary capillary O_2 tension ($P\acute{c}_{O_2}$) being equal to the P_{AO_2}.

The $\dot{Q}s/\dot{Q}t$ was calculated from the following modified equation:[11]

$$\frac{\dot{Q}s}{\dot{Q}t} = \frac{0.0031\ (P_{AO_2} - Pa_{O_2})}{0.0031\ (P_{AO_2} - Pa_{O_2}) + Ca_{O_2} - C\bar{v}_{O_2}},$$

where P_{AO_2} is calculated from the alveolar/air equation by assuming a respiratory exchange quotient of 0.76.[12] The $\dot{V}_{O_2}$ was calculated as the product of $\dot{Q}t$ and arterial-mixed venous O_2 content difference ($Ca_{O_2} - C\bar{v}_{O_2}$).

a: arterial blood
$\acute{c}$: capillary blood
$\bar{v}$: mixed venous blood
A: alveolar gas
BT: body temperature
CI: cardiac index
A-aDO_2: alveolar-arterial tension difference
Ca_{O_2}: arterial O_2 content
$C\acute{c}_{O_2}$: capillary O_2 content
$C\bar{v}_{O_2}$: mixed venous O_2 content
$\dot{Q}s/\dot{Q}t$: true shunt
$\dot{Q}t$: cardiac output
$\dot{Q}_{VA}/\dot{Q}t$: total shunt
S_{O_2}: % saturation of Hb with O_2
$\dot{V}_{O_2}$: O_2 consumption

§Model 113, Instrumentation Laboratories.
†Model DTL: Gilson Medical Electronics, Middleton, Wisconsin.
‡Harvard Apparatus, Millis, Massachusetts.

TABLE 2
Cardiac Output and Blood-Gas Data on Air

		End operation (n = 11)	4 hr later (n = 9)	8 hr later (n = 11)	24 hr later (n = 11)
P_{O_2}, torr	a	73.0 ± 4.7	72.0 ± 6.0	68.0 ± 3.5	62.0 ± 4.3
	$\bar{v}$	37.4 ± 1.8	35.0 ± 2.0	40.0 ± 4.3	34.0 ± 1.9
P_{CO_2}, torr	a	35.8 ± 0.9	31.0 ± 1.0	34.1 ± 1.1	34.5 ± 1.2
	$\bar{v}$	44.0 ± 1.5	40.0 ± 2.0	39.8 ± 1.2	41.4 ± 1.5
pH	a	7.396 ± 0.024	7.471 ± 0.020	7.463 ± 0.014	7.485 ± 0.071*
	$\bar{v}$	7.348 ± 0.024	7.412 ± 0.022	7.425 ± 0.013	7.433 ± 0.008*
S_{O_2}, %	a	92.7 ± 1.4	93.0 ± 3.0	93.7 ± 1.1	91.3 ± 1.8
	$\bar{v}$	66.7 ± 3.0	66.0 ± 5.0	68.6 ± 3.3	65.8 ± 3.5
C_{O_2} vol %	a	16.4 ± 0.9	15.6 ± 1.1	15.8 ± 1.1	15.6 ± 0.9
	$\bar{v}$	11.8 ± 0.7	10.8 ± 1.0	11.5 ± 0.9	11.0 ± 0.7
Ca-$C\bar{v}_{O_2}$, vol %		4.7 ± 0.5	4.8 ± 1.0	4.4 ± 0.6	4.5 ± 0.6
A-aD_{O_2}, torr		32.9 ± 4.2	40.0 ± 6.0	40.0 ± 4.1	46.0 ± 4.4
$\dot{Q}_{VA}/\dot{Q}t$ x 100, %		15.7 ± 3.3	14.0 ± 3.0	16.0 ± 2.7	22.0 ± 4.4
$\dot{V}_{O_2}$, ml/min/sq m		161.0 ± 32.5	115.0 ± 14.0	113.0 ± 19.0	131.0 ± 21.6
CI, L/min/sq m		3.4 ± 0.4	2.6 ± 0.2	2.8 ± 0.4	2.9 ± 0.2
BT, C		36.4 ± 0.6	37.8 ± 0.1	37.2 ± 0.1	37.0 ± 0.1

Mean ± SE.

*Significant as compared to end operation.

Statistical significance was determined by Student's *t*-test for unpaired data.

RESULTS

Mean values and standard error for all variables are shown in tables 2 and 3. No statistical significance at different times was found except increased pH at 24 hours. Metabolic alkalosis after open-heart surgery has been discussed elsewhere.[1]

Using the pooled values, factors affecting A-aD_{O_2} were examined. A positive linear correlation was observed between A-aD_{O_2} and $\dot{Q}_{VA}/\dot{Q}t$ ($r=0.863$, $p<0.01$) or $\dot{Q}s/\dot{Q}t$ ($r=0.516$, $p<0.01$). Two regression lines were derived from the data: $Y=40X-341.2$ and $Y=1.77X+10.39$ on air and 100% O_2, respectively, where Y = A-aD_{O_2}, $X=\dot{Q}_{AV}/\dot{Q}t$ or $\dot{Q}s/\dot{Q}t$ (fig 1). There was no significant difference between $\dot{Q}_{VA}/\dot{Q}t$ and $\dot{Q}s/\dot{Q}t$ at any postoperative period.

No significant correlation was found between CI and $\dot{Q}_{AV}/\dot{Q}t$ ($r=0.05$, $p>0.1$) or $\dot{Q}s/\dot{Q}t$ ($r=0.175$, $p>0.05$) nor between CI and A-aD_{O_2} either on air or 100% O_2.

However, when values were arbitrarily divided into 2 $\dot{Q}_{VA}/\dot{Q}t$ groups—(I) >11% and (II) <10% (fig 2)—there was an inverse correlation in group I between A-aD_{O_2} and CI ($r=-0.502$, $p<0.01$), the regression line being $Y=-29.4X+131.4$ on logarithmic graph, where $Y=\log_{10}$ (A-aD_{O_2}) and $X=\log_{10}$ (CI). This equation was transformed into $Y=288X^{-1.864}$ on arithmetic graph, where Y = A-aD_{O_2} and X = CI ($2\leqq X\leqq 6$), and appeared as a curved line fitting the values in figure 2. There was no significant correlation in group II between A-aD_{O_2} and CI ($r=-0.118$, $p>0.1$), nor was a consistent relation between A-aD_{O_2} and CI detectable, although the same division of values according to the amount of $\dot{Q}s/\dot{Q}t$ was made.

Values at the end of the surgical procedure and at 8 and 24 hours postoperatively were also divided into 2 groups: (I) with Pa_{O_2} values <65 torr and (II) Pa_{O_2} >65

TABLE 3
Cardiac Output and Blood-Gas Data on 100% O_2

		End operation (n = 11)	4 hr later (n = 9)	8 hr later (n = 11)	24 hr later (n = 11)
Po_2, torr	a	443.0 ± 23.4	462.0 ± 15.0	448.0 ± 26.0	364.0 ± 40.2
	$\bar{v}$	51.0 ± 2.9	46.0 ± 2.0	46.0 ± 3.2	46.0 ± 3.0
Pco_2, torr	a	35.6 ± 0.7	33.0 ± 1.0	34.5 ± 1.2	38.3 ± 1.7
	$\bar{v}$	44.2 ± 1.6	41.0 ± 2.0	40.8 ± 1.5	44.8 ± 1.4
pH	a	7.394 ± 0.027	7.453 ± 0.018	7.447 ± 0.022	7.449 ± 0.013*
	$\bar{v}$	7.338 ± 0.027	7.398 ± 0.019	7.392 ± 0.017	7.408 ± 0.010*
So_2, %	a	100	100	100	100
	$\bar{v}$	81.0 ± 2.9	80.0 ± 3.0	78.3 ± 4.2	79.2 ± 3.4
Co_2, vol %	a	18.7 ± 1.0	18.3 ± 1.2	18.1 ± 1.2	18.0 ± 0.9
	$\bar{v}$	14.1 ± 0.8	13.5 ± 0.8	13.1 ± 0.9	13.3 ± 0.7
Ca-C$\bar{v}o_2$, vol %		4.6 ± 0.7	4.8 ± 0.8	5.0 ± 1.0	4.7 ± 0.7
A-aDo_2, torr		234.0 ± 23.3	219.0 ± 14.0	231.0 ± 25.5	311.0 ± 39.4
$\dot{Q}s/\dot{Q}t$ x 100, %		16.0 ± 2.3	14.0 ± 2.0	14.0 ± 1.7	19.0 ± 1.8
$\dot{V}o_2$, ml/min/sq m		128.0 ± 14.4	122.0 ± 17.0	134.0 ± 28.3	137.0 ± 28.1
CI, L/min/sq m		3.2 ± 0.5	2.7 ± 0.3	2.8 ± 0.4	2.9 ± 0.3
BT, C		35.9 ± 0.4	37.8 ± 0.1	37.3 ± 0.2	37.1 ± 0.1

Mean ± SE.
*Significant as compared to end operation.

torr while breathing air (table 4). There was a significant difference in $Cao_2 - C\bar{v}o_2$ between the 2 groups both on air and 100% O_2. Group I was characterized by higher $\dot{Q}_{VA}/\dot{Q}t$ than group II, even though the $\dot{Q}s/\dot{Q}t$ was essentially the same.

DISCUSSION

In our previous study,[1] a gradual fall in Pao_2, whether breathing 40% O_2 or air, was consistently observed and indicated the need for further study on factors affecting A-aDo_2.

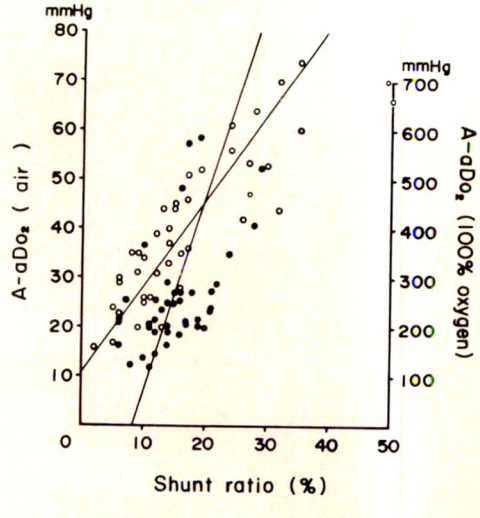


FIG 1. Relationship between A-aDo_2 and intrapulmonary shunt when breathing air ($\dot{Q}_{VA}/\dot{Q}t$, open circles) or 100% O_2 ($\dot{Q}s/\dot{Q}t$, solid circles).

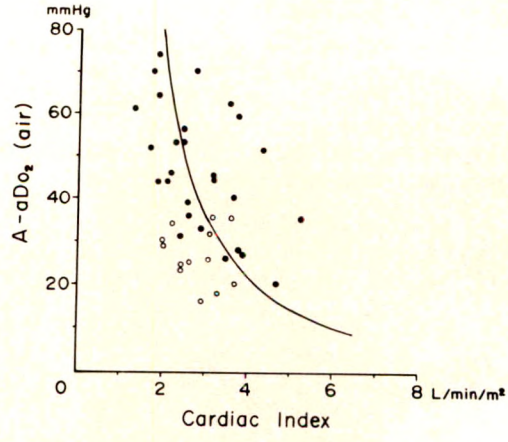


FIG 2. Relationship between A-aDo_2 and cardiac index. Solid circles = values with $\dot{Q}_{VA}/\dot{Q}t$ >11% and open circles = <10%. Curve was derived, when $\dot{Q}_{VA}/\dot{Q}t$ was >11%, from equation:

$Y = 288X^{-1.864}$ $(2 \leqq X \leqq 6)$, Y = A-aDo_2
X = cardiac index

TABLE 4
All Parameters Obtained at End of Operation and at 8 and 24 Hours Postoperatively (Mean ± SE)

	Breathing air		Breathing 100% O_2	
	Low Pa_{O_2}* group (n = 14)	High Pa_{O_2} group† (n = 19)	Low Pa_{O_2}* group (n = 14)	High Pa_{O_2} group† (n = 19)
Pa_{O_2}	53 ± 2	78 ± 2‡	363 ± 38	467 ± 14‡
$P\bar{v}_{O_2}$	32 ± 1	38 ± 1‡	41 ± 3	51 ± 2‡
Ca_{O_2} - $C\bar{v}_{O_2}$	5.4 ± 0.6	3.9 ± 0.3‡	6.5 ± 0.8	3.8 ± 0.2‡
A-aD_{O_2}	54 ± 2	29 ± 2‡	314 ± 37	205 ± 14‡
$\frac{\dot{Q}_{VA} \text{ or } \dot{Q}_s}{\dot{Q}t}$ x 100	28 ± 3	11 ± 1‡	15 ± 2	15 ± 1
CI	3.0 ± 0.4	3.1 ± 0.2	2.6 ± 0.3	3.0 ± 0.2
$\dot{V}_{O_2}$	156 ± 28	121 ± 14	159 ± 26	117 ± 14
BT	36.5 ± 0.4	37.2 ± 0.2	36.6 ± 0.4	37.2 ± 0.2

*<65 torr.
†>65 torr.
‡Significant ($p<0.05$) between low and high Pa_{O_2} group.

Intrapulmonary Shunt. — Marshall and Wyche[7] indicated that postoperative hypoxemia may be divided into early and late types. Early hypoxemia progressively improved to normal within 3 to 4 hours postoperatively, suggesting that anesthesia contributed to increase in intrapulmonary shunt during the early postoperative period. Such an improvement was not observed in our present study.

Our results are in partial agreement with those of Colgan and Mahoney,[4] who also observed no appreciable effect of anesthesia on $\dot{Q}_{VA}/\dot{Q}t$ or $\dot{Q}s/\dot{Q}t$ at 1 to 4 hours following major abdominal surgery. We believe that in this study, anesthesia did not contribute significantly to intrapulmonary shunt. As expected, a positive linear correlation was obtained between A-aD_{O_2} and $\dot{Q}_{VA}/\dot{Q}t$ or $\dot{Q}s/\dot{Q}t$. Several investigators[6,8,13,14] have emphasized atelectasis or ventilation/perfusion inequalities as the primary cause of increased A-aD_{O_2}. The present study is compatible with the report of Hedley-Whyte,[6] who concluded that the most important single cause of postoperative intrapulmonary shunt in cardiac patients was atelectasis as evidenced by the presence of large $\dot{Q}s/\dot{Q}t$ and suggested that hypoxemia was generally present after all major operations.

Our finding of no significant difference between $\dot{Q}_{VA}/\dot{Q}t$ and $\dot{Q}s/\dot{Q}t$ at any postoperative period corroborates those of Muneyuki[9] and of Markello and associates.[15] The latter proposed that this fact may be due to an area of low ventilation/perfusion ratio becoming atelectatic while breathing 100% O_2. This proposal awaits further study.

Cardiac Output.—Kelman[2] theorized that reduction in $\dot{Q}t$ alone may account for increase in A-aD_{O_2} without changes in the underlying shunt. Subsequently, Prys-Roberts' group[16] confirmed Kelman's study in anesthetized man, and Modell and Milhorn[17] observed that a reduction in $\dot{Q}t$ produced an increase in A-aD_{O_2} in thoracotomized dogs. These studies indicated that the alteration of $\dot{Q}t$ must be considered as a significant factor affecting arterial oxygenation. The effect of altered $\dot{Q}t$ on arterial oxygenation can be predicted when $\dot{V}_{O_2}$ and intrapulmonary shunt remain constant.

The following is derived from shunt and Fick equations:

$$C\acute{c}_{O_2} - Ca_{O_2} = \frac{\dot{V}_{O_2}}{\dot{Q}t} \times \frac{R}{1\text{-}R}$$

where R is $\dot{Q}_{VA}/\dot{Q}t$ or $\dot{Q}s/\dot{Q}t$. Using this formula, Philbin[5] predicted the magnitude of decrease in Ca_{O_2} associated with the reduction of $\dot{Q}t$. However, when the content difference $C\acute{c}_{O_2}$ —Ca_{O_2} is converted to tension difference A-aD_{O_2}, the inverse relationship to $\dot{Q}t$ is hyperbolic while breathing 100% O_2 but assumes a complex nonlinear form, in consequence of the shape of the O_2-dissociation curve, while breathing air. Although some observers[3-5] reported no consistent relationship between $\dot{Q}t$ and A-aD_{O_2}

during the postoperative period, we found an inverse correlation when $\dot{Q}_{VA}/\dot{Q}t$ was >11%, but none when <10%.

The failure to demonstrate correlation between A-aDo_2 and $\dot{Q}t$ with 100% O_2 warrants further explanation. One possible explanation is that a change in $\dot{Q}t$ may be accompanied by the same directional change in $\dot{Q}s/\dot{Q}t$ as that which counteracts to low Pao_2 produced by the reduction of $\dot{Q}t$.[18-20] We are unaware of any report regarding the correlation between $\dot{Q}t$ and $\dot{Q}_{VA}/\dot{Q}t$ in postoperative patients.

Marshall and Wyche[7] state that $\dot{Q}t$ is not an important determinant of intrapulmonary shunt. Discrepancy among these investigations may be due to complex interrelationships between $\dot{Q}t$, intrapulmonary shunt, and $\dot{V}o_2$. The present study, however, clearly showed that low CI (below 2.5 L/min/sq m) significantly contributed to enlargement of A-aDo_2 when $\dot{Q}_{VA}/\dot{Q}t$ was large.

Oxygen Consumption.—In spite of the great interest in the effect of $\dot{V}o_2$ on arterial oxygenation after operations, little data exist on the relationship between $\dot{V}o_2$ and A-aDo_2. Our low Pao_2 group showed a significantly larger $Cao_2 - C\bar{v}o_2$ and higher $\dot{Q}_{VA}/\dot{Q}t$ than the high Pao_2 group. However, there was no significant difference in $\dot{Q}s/\dot{Q}t$ between the 2 groups. Therefore, low Pao_2 may be one of the factors related to the widening $Cao_2 - C\bar{v}o_2$.

Although no statistically significant difference in $\dot{V}o_2$ was found between the 2 groups, the mean value in the low Pao_2 group was greater than in high Pao_2 group, as compared with the changes in CI. Therefore, it is suggested that a $\dot{Q}t$ which is not sufficient for metabolic demand may contribute to low Pao_2. An increase in the $\dot{V}o_2$ in the postoperative period of open-heart surgery may be caused by rise in body temperature, shivering, restlessness, an increase in the work of breathing, or a change in pH. However, we found no significant difference in such factors increasing in $\dot{V}o_2$ between the 2 groups.

In noncardiac patients,[3] there was no correlation between $\dot{V}o_2$ and Pao_2, with or without shivering, in the early postoperative period, since increased $\dot{V}o_2$ may be counteracted by increased $\dot{Q}t$. On the other hand, Kirklin and Rastelli[20] pointed out that $\dot{Q}t$ relative to metabolic demand is reduced soon after cardiac surgery, a finding comparable to our results, in that $\dot{V}o_2$ is larger in the low Pao_2 group, and may be a possible factor in increasing A-aDo_2 after open-heart surgery.

In our study the low Pao_2 group showed a higher $\dot{Q}_{VA}/\dot{Q}t$ than the high Pao_2 group, even though the $\dot{Q}s/\dot{Q}t$ was essentially the same in the 2 groups. These differences may be the result of impaired diffusion due to relatively low inspired O_2 concentration.

It has been generally accepted that diffusion gradient has a significant role in producing A-aDo_2 only when the PAo_2 is well below normal. Fordham[14] examined the diffusion effect in patients after open-heart surgery and concluded that the pulmonary diffusion effect, if present, played only a small part in hypoxemia after such operations. However, Hedley-Whyte[6] suggested that if the distribution of ventilation is sufficiently uneven, one must assume that a diffusion effect adds to the shunt because in the least ventilated alveoli, the PAo_2 may be sufficiently low, or the alveolar membranes sufficiently thickened, to establish a diffusion gradient. We prefer to think of this manifestation as a result of uneven distribution of ventilation.

We conclude that intrapulmonary shunt plays an important role in increasing postoperative A-aDo_2 and causes further development of hypoxia, especially when it is accompanied by a reduction in CI below 2.5 L/min/sq m or by a relative increase in $\dot{V}o_2$ not compensated by an increase in $\dot{Q}t$.

REFERENCES

1. Sari A, Sugi S, Oda T, et al: Respiratory factors in the management of patients after open-heart sugery. Anesth & Analg 50:1028-1035, 1971

2. Kelman GR, Nunn JF, Prys-Roberts C, et al: The influence of cardiac output on arterial oxygenation: a theoretical study. Br J Anaesth 39:450-458, 1967

3. Bay J, Nunn JF, Prys-Roberts C: Factors influencing arterial Po_2 during recovery from anaesthesia. Br J Anaesth 40:398-406, 1968

4. Colgan FJ, Mahoney PD: The effects of major surgery on cardiac output and shunting. Anesthesiology 31:213-221, 1969

5. Philbin DM, Sullivan SF, Bowman FO Jr, et al: Postoperative hypoxemia: contribution of the cardiac output. Anesthesiology 32:136-142, 1970

6. Hedley-Whyte J, Corning H, Laver MB, et al: Pulmonary ventilation-perfusion relations after heart valve replacement of repair in man. J Clin Invest 44:406-416, 1965

7. Marshall BE, Wyche MQ Jr: Hypoxemia during and after anesthesia. Anesthesiology 37:178-209, 1972

8. Geha AS, Sessler AD, Kirklin JW: Alveolar-arterial oxygen gradients after open intracardiac surgery. J Thorac Cardiovasc Surg 51:609-615, 1966

9. Muneyuki M, Ueda Y, Urabe N, et al: Oxygen breathing and $\dot{Q}s/\dot{Q}t$ during postoperative pain relief in man. Can Anaesth Soc J 19:230-238, 1972

10. Severinghaus JW: Blood gas calculator. J Appl Physiol 21:1108-1116, 1966

11. Finley TN, Lenfant C, Haab P, et al: Venous admixture in the pulmonary circulation of anesthetized dog. J Appl Physiol 15:418-424, 1960

12. Sturridge MF, Theye RA, Fowler WS, et al: Basal metabolic rate after cardiovascular surgery. J Thorac Cardiovasc Surg 47:298-307, 1964

13. McLlenahan JB, Young WE, Sykes MK: Respiratory changes after open-heart surgery. Thorax 20:545-554, 1965

14. Fordham RMM: Hypoxemia after aortic valve surgery under cardiopulmonary bypass. Thorax 20:505-509, 1965

15. Markello R, Winter P, Olszowka A: Assessment of ventilation-perfusion inequalities by arterial-alveolar nitrogen differences in intensive-care patients. Anesthesiology 37:4-15, 1972

16. Prys-Roberts C, Kelman GR, Greenbaum R: The influence of circulatory factors on arterial oxygenation during anaesthesia in man. Anaesthesia 22:257-275, 1967

17. Modell H, Milhorn HT Jr: Quantitation of factors affecting the alveolar-arterial Po_2 difference in thoracotomy. Anesthesiology 37:592-599, 1972

18. Yamamura H, Kaito K, Ikeda K, et al: The relationship between physiologic shunt and cardiac output in dogs under general anesthesia. Anesthesiology 30:406-413, 1969

19. Hasse J, Wolff G, Grädel E: The significance of cardiac output for the interrelation and intrapulmonary right-left-shunt following thoracotomies. Anaesthesist 23:1-4, 1974

20. Kirklin JW, Rastelli GC: Low cardiac output after open intracardiac operation. Prog Cardiovasc Dis 10:117-122, 1967

Hepatic Clearance of Lidocaine During N_2O Anesthesia in Dogs

ROBERT G. BURNEY, MD*
COSMO A. DiFAZIO, PhD, MD†
Charlottesville, Virginia‡

Lidocaine catabolism under N_2O anesthesia was evaluated in 5 dogs given a lidocaine infusion of 2 mg/kg/min for 20 minutes. Comparison of results with those of a prior similar study with halothane anesthesia showed catabolism of lidocaine to be significantly faster in the animals given N_2O. The extraction ratio for lidocaine, which did not vary with its arterial concentration, was significantly lower with halothane than with N_2O. Decreased hepatic catabolism of drugs such as lidocaine should be anticipated in patients anesthetized with potent inhalation agents such as halothane.

LIDOCAINE is frequently administered together with general anesthetics, either for the enhancement of the anesthetic state or to control cardiac arrhythmias. The resultant blood level of lidocaine is a function principally of the dose administered, the distribution of the drug, and the rate of hepatic elimination. Hepatic elimination of lidocaine can be changed by alterations in hepatic blood flow[1,2] and drug effects on hepatic enzymes.[3,4] Although inhalational anesthetic agents are known to affect hepatic blood flow[5,6] and the catabolism of drugs,[7,8] the effect of concomitantly administered inhalational agents on the catabolism of lidocaine has not been defined.

This study was designed to determine if the disappearance of lidocaine during N_2O anesthesia differs from that observed under halothane,[3] and if lidocaine extraction varies with the blood concentration of the drug itself.

METHOD

Five mongrel dogs weighing 15 to 20 kg were anesthetized with an 80% N_2O-O_2 (0.43 MAC)-curare technic. Ventilation was controlled with an Emerson ventilator. The femoral artery was cannulated and the abdomen opened. A catheter was passed from the external jugular into a hepatic vein under direct vision. Arterial blood pressure was recorded on a Model 7 Grass polygraph. A fluid load of 500 ml of 5% dextrose/lactated Ringer's solution was given before the experiment. Heparinized blood samples (6 ml) were drawn from the femoral artery (considered equivalent to blood in the hepatic artery) and the hepatic vein in a control state, and 30, 60, 90, and 120 minutes after a 2 mg/kg/min dose of lidocaine was infused over a 20-minute period.

Arterial blood gases were determined using a Radiometer Blood Gas Analyzer, with the $Paco_2$ maintained at 25 to 30 torr. Lidocaine was quantitated with a Hewlett-Packard 5750 gas chromatograph equipped with a flame-ionization detector, using a previously described method.[9]

Extraction of lidocaine by the liver was calculated from the concentration gradient of the drug across the liver and is expressed

*Assistant Professor of Anesthesiology.
†Professor of Anesthesiology.
‡University of Virginia Medical Center, Charlottesville, Virginia 22903.

Paper received: 8/12/75
Accepted for publication: 12/1/75

TABLE 1
Arterial and Hepatic Venous Lidocaine Blood Concentrations (μg/ml) Following an IV Bolus Under N_2O-O_2 Anesthesia

Time, min	30		60		90		120	
Dog	Arterial	Hepatic venous	Arterial	Hepatic venous	Arterial	Hepatic venous	Arterial	Hepatic venous
1	4.57	1.36	3.13	1.11	2.15	0.90	1.47	0.73
2	3.90	2.03	2.92	1.59	2.19	1.24	1.64	0.97
3	2.74	1.93	1.87	1.03	1.28	0.55	0.88	0.30
4	4.09	2.13	2.80	1.32	1.92	0.81	1.32	0.50
5	4.12	1.05	2.91	0.76	2.06	0.54	1.45	0.39
Means	3.88	1.70	2.73	1.16	1.92	0.81	1.35	0.58
SD	0.68	0.47	0.49	0.31	0.37	0.29	0.29	0.27

as a fraction of drug removed. Drug disappearance data was plotted on semilog coordinates by the least-squares technic on a programmable calculator. Significant differences of blood-lidocaine concentration at 30, 60, and 120 minutes in the N_2O and halothane experiments and of the k (disappearance rate constant) values calculated from the disappearance curves were determined by Student's t-test. The measured concentrations of lidocaine existing after the early distributional phase in each study were fitted to the equation $[L] = ae^{-kt}$.

RESULTS (table 1 and figure)

The disappearance of lidocaine in the presence of N_2O was significantly faster than that previously reported in dogs anesthetized with halothane. The mean ($\pm$ SD) of the k values with N_2O in this experiment was 0.0122 ± 0.0013 (n=5). In contrast, the mean k value for all dogs previously studied using halothane was 0.0081 ± 0.003 (n=5), k values significantly different at $p<0.05$. The mean extraction ratio of lidocaine during administration of N_2O-curare was 0.57 $\pm$ 0.11. This is more than a twofold increase over the values previously obtained during halothane anesthesia. The hepatic extraction ratio for lidocaine during N_2O anesthesia was unaffected by lidocaine concentration over a wide range.

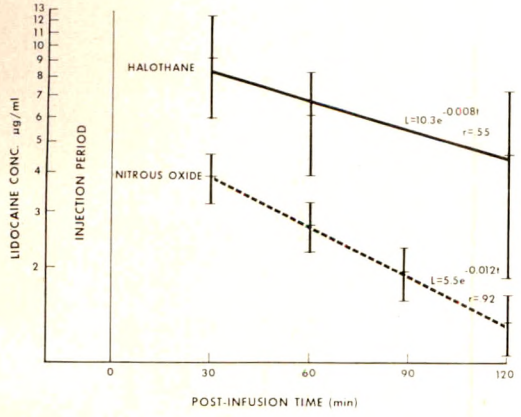


FIGURE. Lidocaine disappearance curves (arterial blood). The early distribution phase is omitted. Blood concentrations were significantly lower when N_2O was the anesthetic ($p<0.01$ at 30 min, $p<0.05$ at 60 and at 120 min).

DISCUSSION

The only significant differences between the 2 groups studied, other than the choice of anesthetic agent were: (1) the halothane group breathed spontaneously, with $Paco_2$ between 40 and 50 torr, whereas the N_2O animals were ventilated, with $Paco_2$ between 25 and 30 torr, and (2) the N_2O group also received curare while the halothane group received only succinylcholine for intubation.

Mechanical ventilation decreases splanchnic blood flow, probably on a mechanical basis.[6] However, this should decrease the differences between our study groups. Carbon dioxide is known to affect splanchnic flow.[5,6] However, the higher $Paco_2$ during halothane anesthesia should increase hepatic flow.[6] Muscle relaxants per se are not known to affect hepatic flow. Ganglionic blocking agents do not affect splanchnic resistance,[5] and this property of curare should not have affected our results. Thus, the major differences between the present experiment and the previous study should tend to decrease the observed differences between the 2 groups.

The disappearance of lidocaine from blood after the initial distribution phase is primarily dependent on hepatic removal. Thus the differences observed between the removal rate during halothane and N_2O anesthesia could result from alterations in hepatic removal through effects on hepatic blood flow or on the hepatic enzymes. Hepatic enzymes in turn may be affected by membrane permeability, availability of cofactors, enzyme saturation, and inhibition by other drugs.

Lidocaine removal has been shown to be directly affected by hepatic blood flow. Stenson's group[1] observed that in cardiac patients receiving a constant IV infusion of lidocaine, higher lidocaine blood levels occurred when cardiac output (and presumably hepatic blood flow) was decreased. Benowitz and associates[2,10] observed that with the decreased hepatic blood flow produced by norepinephrine infusion, a decreased rate of hepatic removal of lidocaine occurred. Conversely, an increased rate of hepatic removal of lidocaine was produced in the presence of an increased hepatic blood flow resulting from the infusion of isoproterenol.

Halothane[6,11,12] and cyclopropane[13] have been shown to reduce hepatic blood flow in man and animals, one group[12] suggesting that blood flow decreases with increasing depth of anesthesia. Certainly part of the difference in the rate of hepatic removal of lidocaine with N_2O or halothane present can be attributed to the differences in hepatic blood flow produced by the inhalational anesthetics. While absolute values of changes in hepatic blood flow in animals with any fixed anesthetic concentration remains to be defined, an approximation might be obtained by assuming that the hepatic blood flow in animals receiving halothane is 25% less than in those receiving N_2O, a value comparable to the 20 to 30% differences observed in anesthetized human volunteers.[6,13] Disappearance rate and half-life (T_{50}) calculations for lidocaine under such conditions (table 2) result in a T_{50} of 77 minutes for lidocaine and differs from the 99-minute T_{50} calculated from the prior halothane experiment. It seems plausible that the decreased disappearance rate for lidocaine under halothane anesthesia is contributed to by factors other than the reduction in hepatic blood flow.

Inhalational anesthetics have in addition been suspected of altering the catabolism of many drugs. A high concentration of the anesthetics in the lipid-rich microsomes principally involved in drug biotransformation is to be expected on the basis of lipid solubility of the anesthetics. Baekland and Greene[14] demonstrated that pentobarbital metabolism by liver homogenates was decreased by the addition of diethyl ether. Brown[7,15] documented *in vitro* dose-dependent inhibition of oxidative metabolism of barbiturates and aminopyrine by both halothane and methoxyflurane, while Sawyer and associates[8] suggested that an increase in halothane concentration decreases hepatic halothane removal by either enzyme saturation or substrate inhibition.

The differences in lidocaine disappearance found in the present studies suggest that halothane may decrease the removal of lidocaine by an effect on hepatic microsomes in addition to the expected effect on hepatic blood flow, although the exact mechanism remains to be defined, and may be the noncompetitive dose-dependent effect seen by Brown[7] with halothane on barbiturate destruction. However, regardless of which mechanism dominates, decreased hepatic removal of drugs such as lidocaine should be anticipated when administered to patients anesthetized with potent inhalational anesthetic agents.

TABLE 2

Values of k^* for N_2O-Anesthetized and Halothane-Anesthetized Animals

Anesthetic	Rate constant (k)	Half-life (T_{50}), min
N_2O (observed values)	0.012	59
N_2O (corrected for an assumed 25% reduction in $\dot{Q}$)	0.009	77
Halothane (observed values)	0.007	99

*k = disappearance rate constant; measured from least-square plot (figure).

For a theoretical circumstance in which the liver blood flow of the N_2O anesthetized animals is reduced by an arbitrary 25%, k is calculated from the equation $k = \frac{\dot{V}_d}{\dot{Q}.E}$, assuming no change in $\dot{V}_d$ and E occurs with the reduction in flow. ($\dot{V}_d$ = volume of distribution, $\dot{Q}$ = hepatic blood flow, E = extraction fraction.) The half-life (T_{50} is calculated from the equation $T_{50} = \frac{\ln 2}{k} = \frac{0.693}{k}$.

REFERENCES

1. Stenson RE, Constantino RT, Harrison DC: Inter-relationships of hepatic blood flow, cardiac output, and blood levels of lidocaine in man. Circulation 43:205-211, 1971

2. Benowitz N, Forsyth RP, Melmon KL, et al: Lidocaine disposition on kinetics in monkey and man. II. Effects of hemorrhage and sympathomimetic drug administration. Clin Pharmacol Ther 16:99-109, 1974

3. DiFazio CA, Brown RE: Lidocaine metabolism in normal and phenobarbital-pretreated dogs. Anesthesiology 36:238-243, 1972

4. Heinonin J: Influence of some drugs on toxicity and rate of metabolism of lidocaine and mepivacaine. Ann Med Exp Biol Fenn 44 (suppl 3):1-43, 1966

5. Cooperman LH: Effects of anaesthetics on the splanchnic circulation. Br J Anaesth 44:967-970, 1972

6. Epstein RM, Deutsch S, Cooperman LH, et al: Splanchnic circulation during halothane anesthesia and hypercapnia in normal man. Anesthesiology 27:654-661, 1966

7. Brown BR Jr: Enzymatic activity and biotransformation of anesthetics. Int Anesthesiol Clin 12:25-34, 1974

8. Sawyer DC, Eger EI II, Bahlman SH, et al: Concentration dependence of hepatic halothane metabolism. Anesthesiology 34:230-235, 1971

9. DiFazio CA, Brown RE: The analysis of lidocaine and its postulated metabolites. Anesthesiology 34:86-88, 1971

10. Benowitz N, Forsyth RP, Melmon KL, et al: Lidocaine disposition kinetics in monkey and man. I. Prediction by a perfusion model. Clin Pharmacol Ther 16:87-97, 1974

11. Juhl B, Einer-Jensen N: Hepatic blood flow and cardiac output during halothane anaesthesia: an animal study. Acta Anaesthesiol Scand 18:114-122, 1974

12. Thulin L, Andreen M, Irestedt L: Effect of controlled halothane anaesthesia on splanchnic blood flow and cardiac output in the dog. Acta Anaesthesiol Scand 19:146-153, 1975

13. Price HL, Cooperman LH, Clement AJ, et al: Splanchnic circulation during cyclopropane anesthesia in normal man. Anesthesiology 26:312-319, 1965

14. Baekland F, Greene NM: Effect of diethyl ether on metabolism of pentobarbital in rats. Anesthesiology 19:724-732, 1658

15. Brown BR Jr: The diphasic action of halothane on the oxidative metabolism of drugs by the liver. An in vitro study in the rat. Anesthesiology 35:241-246, 1972

The Lateral Sitting Position for Neurosurgery

FRANCISCO GARCIA-BENGOCHEA, MD*
EDWIN S. MUNSON, MD†
JAMES V. FREEMAN, MD‡
Gainesville, Florida‖

Over the past 20 years, more than 300 patients have been anesthetized in the lateral sitting position during neurosurgical procedures in the posterior fossa and the cervical and upper thoracic spine. Since the patient can be placed quickly and easily in the horizontal position, the lateral sitting position has a number of advantages over the conventional sitting position, particularly in the treatment of arterial hypotension and venous air embolism. Furthermore, with the patient in the lateral horizontal position, the surgical procedure can be completed satisfactorily.

DURING the past 20 years, the lateral sitting position has been used satisfactorily for operations in the posterior fossa and the cervical and upper thoracic spine. Since the initial report 19 years ago,[1] a number of technical modifications have been introduced, some of which were reported[2] in 1963 and others of which have been incorporated recently. This paper describes the technic for the anesthesiologist as it is presently carried out and discusses the method as one of the therapeutic measures for managing arterial hypotension and venous air embolism during operations on patients in the sitting position.

DESCRIPTION OF TECHNIC

The main steps of our method are as follows:

1. The patient is placed supine on the operating table (fig 1A) for insertion of intravascular catheters, application of monitoring equipment, induction of anesthesia, and tracheal intubation. Elastic stockings may be applied to the patient's legs.

2. The skull clamp is fixed to the patient's head.

3. The operating table is maximally "flexed" by manipulating the S-handle on the right side of the H-frame, while the seat is kept almost horizontal by simultaneous and proportional motions in the reverse Trendelenburg direction through activation of the T-handle on the left side of the H-frame (fig 1B).

4. The back section is elevated further to about 80° from the horizontal by activating the S-handle on the right side of the H-frame (fig 1C). The flat headrest of the table is removed and replaced by the attachment for the skull clamp (fig 1D).

*Professor of Neurological Surgery.

†Professor of Anesthesiology.

‡Clinical Assistant Professor of Neurological Surgery.

‖Division of Neurological Surgery, Departments of Surgery and Anesthesiology, University of Florida Health Center, Gainesville, Florida 32610.

Paper received: 8/1/75
Accepted for publication: 9/24/75

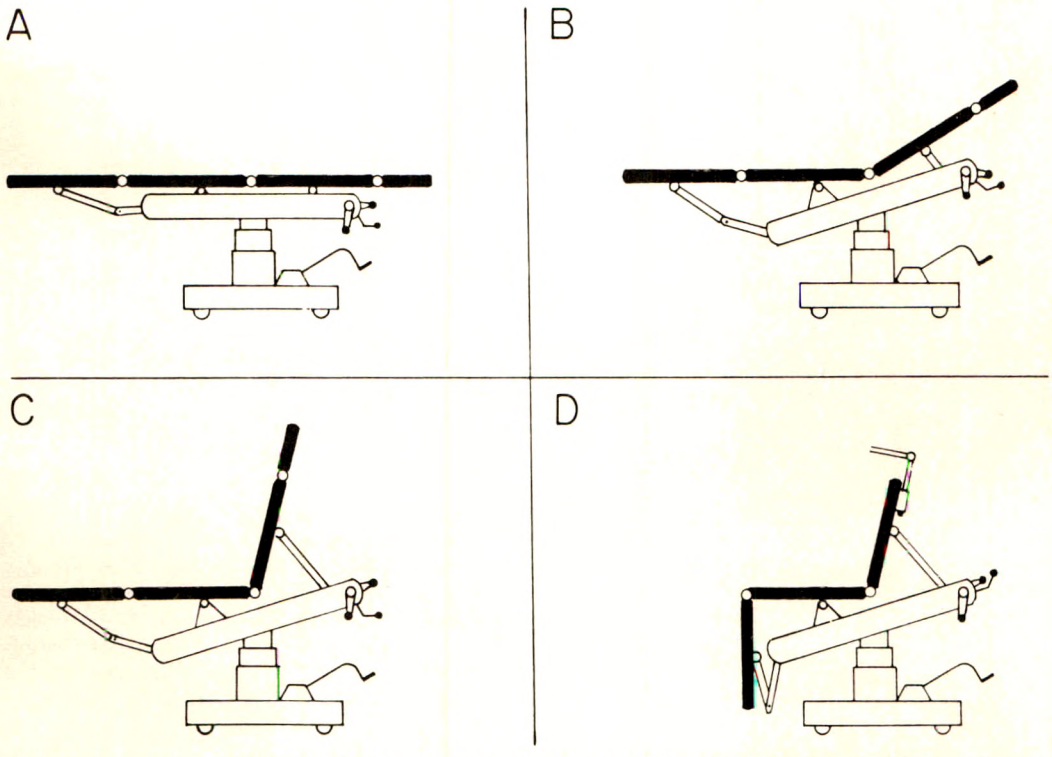


FIG 1. Schematic drawing showing the manipulations required to convert the table H-frame and table top for use with the lateral sitting position (see text for details). The patient is not represented but can easily be imagined.

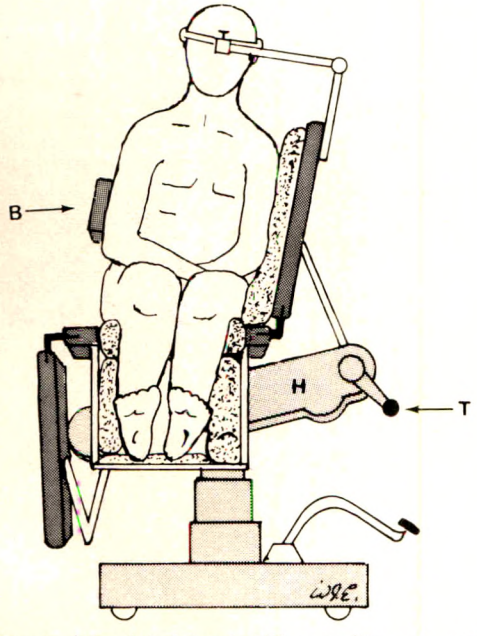


FIG 2. The left lateral sitting position, as seen from left side of operating table. H = main movable frame of table. T = handle for moving in Trendelenburg direction and reverse. B = backrest.

5. While the surgeon or one assistant manually holds the head, the patient is rotated to become perpendicularly oriented to the long axis of the operating table. The shoulder and arm leaning against the back section of the operating table are thoroughly padded with foam rubber or similar materials. In children and short patients, additional padding is placed under the buttocks to elevate the head to the level of the skull clamp attachment.

6. The special backrest B* (fig 2 and 3) is attached to the side rail of the back section and the operating table is tilted about 5 to 10° toward the dorsum of the patient.

7. The skull clamp is connected to the table attachment and the head fixed in the desired position (fig 2 and 3).

8. The lower extremities are well padded to protect them from pressure phenomena against the supporting surfaces, as well as from pressure against the opposite lower extremity. The legs and feet are supported

*Specifications for the backrest and foot attachment available from author on request.

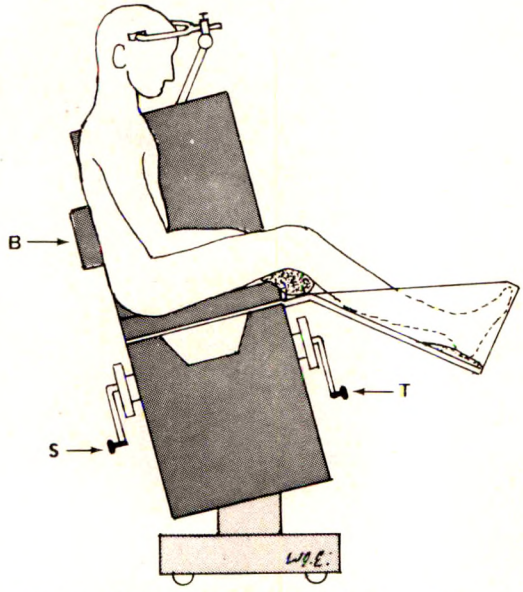


FIG 3. Patient in left lateral sitting position, as seen from foot end of operating table. S = handle for moving back, seat, and foot section of table top. B and T as in figure 2.

by a specially designed foot attachment* (fig 2 and 3). This can be adjusted at different angles of elevation between the plane of the seat section and 90° below it.

*Specifications for the backrest and foot attachment available from author on request.

9. The regular foot section of the operating table is completely flexed, thus transforming the table into the configuration of a chair (fig 1D).

10. A bar for holding the drapes is attached to the side rail of the back section of the operating table at the level of, and in front of, the head. A second bar is attached below the first at the level of the heart for support of pressure transducers (fig 4). When the surgical preparation and draping of the operative field are completed, the drapes are brought over and around the second bar, creating a "tent" that permits excellent access to the patient's face, neck, trunk, and extremities.

Neither instrument tables nor stands, IV poles, or other equipment should have any attachment to the drapes or operating table, but should be placed conveniently so they will not limit or hinder any motions for lowering the head. In the event the head must be lowered, the anesthesiologist manipulates the T-handle for the control of the Trendelenburg motion, bringing the head down toward the horizontal as desired (fig 5). If the table then is too low to allow adequate range of Trendelenburg motion of the H-frame, the pedal for raising the height of the whole table must be activated by the surgeon or one of his assistants to obtain the desired height. The surgical procedure

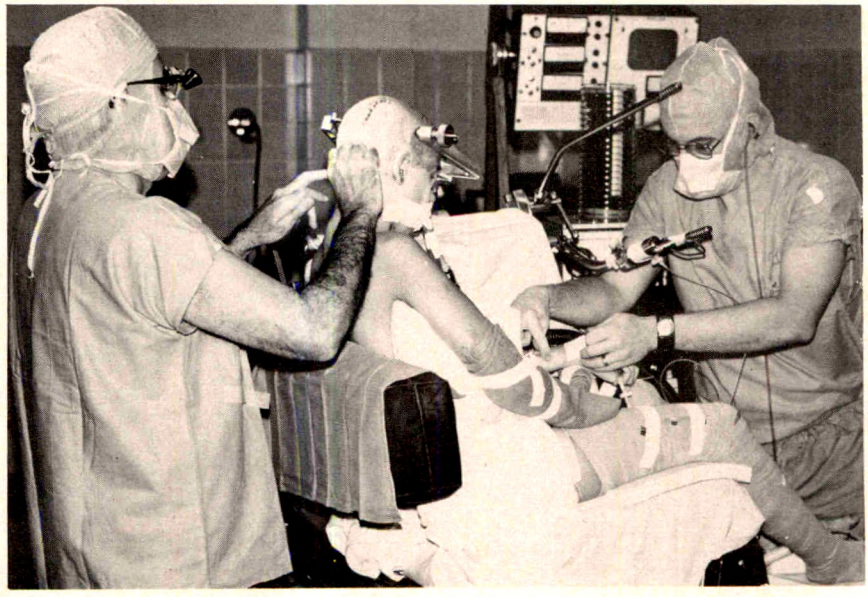


FIG 4. Surgeon (left) and anesthesiologist (right) just before preparing and draping patient for a right suboccipital craniectomy. Backrest and supporting bars for drapes and arterial transducers are shown. Lateral sitting position gives anesthesiologist excellent access both to patient's airway and to monitoring equipment.

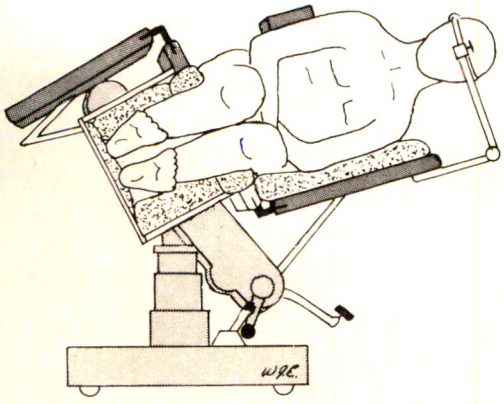


FIG 5. Patient brought down from left lateral sitting position (as shown in fig 2) to an almost complete left lateral horizontal position.

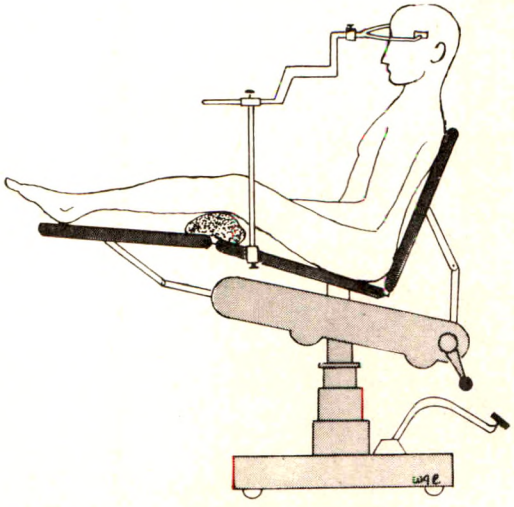


FIG 6. Conventional sitting position for operation in posterior fossa and cervical spine, as seen from left side of operating table.

can be completed in the lateral horizontal position or, if conditions permit, the head can be elevated again toward the vertical position. All these motions are achieved without disturbing the sterile conditions of the surgical field to which the surgeon retains, at all times, direct access, with full control of the wound.

The above description and illustrations refer to the American Sterilizer Company model 1080 operating table; not all other operating tables can be adjusted for this specific use.

COMMENT

For surgical procedures in the posterior fossa and the cervical spine, many neurosurgeons prefer to have the patient in the upright position. If arterial hypotension develops in a patient in the sitting position, one effective means of protecting the brain is to bring the patient to a recumbent position with the head lying on the same horizontal plane as that of the heart. However, when hypotension develops in a patient positioned in the conventional sitting position, as depicted in figure 6, lowering the level of the head can be achieved only by a backward and downward motion of the head, neck, and upper trunk. Thus positioned, the patient is supine, with the operative wound facing the floor. The fundamental conditions of surgical sterility are disrupted and the operative field becomes inaccessible to the surgeon. At best, all that can be accomplished is to protect the field with sterile towels until the situation is under control and the patient is either repositioned and redraped for continuation of surgery, or more commonly, the procedure is terminated and the wound closed.

In contrast, the lateral sitting position can be converted to the lateral horizontal position by simply manipulating the T-handle (fig 5). About 10° more of a head-down position can be gained if the back section of the table is lowered by the S-handle on the right side of the H-frame. This can be accomplished without hazard because the head is attached to the back piece where the neck, trunk, and head can be safely moved together. Further lowering of the head is probably unnecessary.

The position achieved in the lateral, horizontal position (fig 5) is essentially the same as that described by Mount.[3] If the patient's condition permits, operation can be resumed and completed in the lateral position. We have found that being able to move the patient safely and easily from upright to horizontal (and vice versa) is a most practical asset of the method, aimed at protecting the brain from potential ischemic effects of undesirable intraoperative arterial hypotension. Marshall[4] also has advocated the use of the lateral sitting position for the management of venous air embolism.

The left lateral horizontal position, as described above, is similar to that described by Durant's group[5] and evaluated by Oppenheimer and coworkers[6] for the treatment of venous air embolism. However, in patients with lateralized lesions, such as a cerebellopontine-angle tumor on the left

side, there may be advantage in reversing the patient's position on the operating table so that the left operative side is uppermost. Therefore, when the table is placed horizontally, the patient lies in the *right* lateral horizontal position. While this position has been shown in dogs to offer no advantage in the treatment of venous air embolism,[6] the ability to place the patient horizontal (right or left lateral) is of great therapeutic advantage in the management of arterial hypotension, whether secondary to air embolism or to other causes. This position also permits continued exposure of the operative site so that the surgical procedure will not be interrupted.

Over 300 neurosurgical procedures have been performed with the patients in the lateral sitting position. Approximately one-half of these procedures were suboccipital craniectomies and the remainder were cervical and upper thoracic laminectomies. No mortality or serious morbidity could be attributed to the use of this position. In nine instances where patients were placed in the lateral horizontal position for the treatment of hypotension, the arterial pressure was restored to adequate levels. Each operation was completed satisfactorily, with the patient maintained either in the lateral horizontal position or with the head subsequently raised 35 to 80° from the horizontal plane.

ACKNOWLEDGMENT

The authors gratefully acknowledge William J. Embro for preparing the drawings.

REFERENCES

1. Garcia-Bengochea F, Fernandez JC: The lateral sitting position for operations in the posterior fossa and in the cervical and upper thoracic regions of the spine. J Neurosurg 13:520-522, 1956

2. Garcia-Bengochea F, Nash G: Fijacion de la cabeza en la posicion sentada lateral. Acta Neurol Lat Am 9:85-87, 1963

3. Mount LA: The lateral position for operations in the cerebellopontine angle. J Neurosurg 2:460-461, 1945

4. Marshall BM: Air embolus in neurosurgical anaesthesia, its diagnosis and treatment. Can Anaesth Soc J 12:255-261, 1965

5. Durant TM, Long J, Oppenheimer MJ: Pulmonary (venous) air embolism. Am Heart J 33: 269-281, 1947

6. Oppenheimer MJ, Durant TM, Lynch P: Body position in relation to venous air embolism and the associated cardiovascular-respiratory changes. Am J Med Sci 225:362-373, 1953

Inspired Air Temperature with Immersion Heater Humidifiers

KUNNATHU P. GEEVARGHESE, MB, BS, FRCP(C)*
J. ANTONIO ALDRETE, MD, MS†
TARANGINI C. PATEL, MB, BS‡
Louisville, Kentucky§

The temperature of aerosol mixture delivered from 2 types of immersion heater humidifiers was monitored at various sites along the delivery tube. As anticipated, the temperature of the humidified gas decreased as it moved distally from the aerosol generator to the T-adaptor in contact with patient's airway. The immersion heaters with fixed-temperature thermostatic control performed consistently, though most produced inhaled air temperatures higher than desired (>37° C). Immersion heaters with temperature reset features were in general unreliable and invariably gave higher inspired air temperatures with higher settings of the thermostat.

THE place of humidity in inhalation therapy and respiratory care is well established.[1-5] The use of heated humidifiers is common in postanesthesia recovery rooms and intensive care areas for patients with tracheostomy, prolonged endotracheal intubation, and those needing mask O_2 therapy, especially when there are secretion problems.

We employ the Puritan all-purpose nebulizers (model 126-056) with immersion heaters because they provide adequate water content to the inspired air in the form of humidity and aerosol droplets. These versatile units allow O_2 dilution with air. The immersion heater units are interchangeable and are available in 2 models: (1) model TR, with a temperature reset feature on the thermostatic control, and (2) model FT, with a fixed temperature thermostatic control.

From time to time we have noted that the inhaled O_2-air mixtures were too warm for patient comfort. This led us to monitor the temperature of the inspired air in 15 patients, using inhalation systems with heated humidifiers while employing mask or endotracheal tube for delivery of gases. Since the values in these preliminary observations varied from 23.3° to 42.2° C, and in 5 instances we had to discontinue treatment because of high temperatures, a more extensive and detailed study was undertaken.

MATERIAL AND METHODS

Fifteen immersion heaters, less than 1 year old and routinely serviced by the central sterilization unit, were studied. Fixed-temperature models were numbered FT 1 to 8 and temperature-reset models were numbered TR 9 to 16. An O_2 therapy system identical with those used in the clinical

*Associate Professor.
†Professor. Current address: Department of Anesthesiology, University of Colorado School of Medicine, Denver, Colorado.
‡Instructor.
§Department of Anesthesiology, University of Louisville School of Medicine and Veterans Administration Hospital, Louisville, Kentucky 40202.
Paper received: 3/31/75
Accepted for publication: 10/31/75

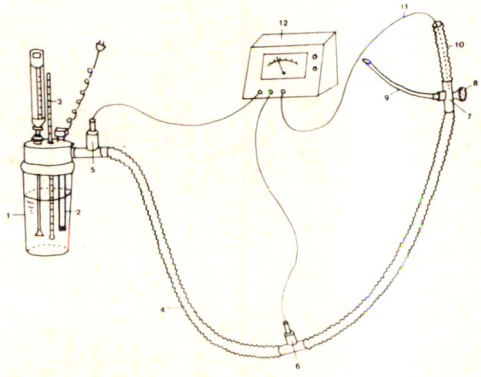


FIG 1. Diagrammatic representation of O_2 therapy system set up for studies. 1. All purpose nebulizer. 2. Immersion heater (FT or TR model). 3. Mercury stem thermometer. 4. Aerosol delivery tube. 5. Nebulizer outlet thermistor probe. 6. Middle of aerosol tubing-thermistor probe. 7. Patient end T-adaptor. 8. Bennett manifold thermometer in patient end T-adaptor. 9. Endotracheal tube on patient end T-adaptor. 10. Expiratory limb. 11. Thermistor probe in patient end T-adaptor. 12. YSI model 47 scanning telethermometer.

situation was set up (fig 1). Temperature of the water bath was measured by an Hg (C) stem thermometer. The corrugated aerosol tubing of approximately 1.9 cm diameter* was 1.5 m long. The distal (patient) end of the tubing was connected with an aerosol T-adaptor† via a manifold thermometer assembly‡.

The expiratory limb of the T-adaptor was 15 cm long and the tracheostomy or endotracheal port received a 9.5 mm Portex clear plastic endotracheal tube. Thermistor telethermometer probes were installed via suitable airtight T-pieces at the outlet of the nebulizer and middle of the aerosol tubing. A third thermistor probe was located inside the T-adaptor at the patient end by inserting it through the expiratory limb. Thus the patient end T-adaptor had 2 temperature sensors to verify each other. The 3 thermistor probes were connected to channels 1 to 3 of a scanning telethermometer§. Temperatures were measured in Fahrenheit and converted to corresponding Celsius values.

The nebulizer was set at an O_2 inflow of 7 L/min and at 40% O_2 air dilution. All immersion FT heaters were tested individually. For each test, the whole equipment was started at room temperature, constantly maintained at 25.6° C and 45% relative humidity. Precautions were taken to ensure that the initial temperature of the system was at control level and that the tubing contained no water accumulation from prior use. Temperature readings were taken at 30 and 60 minutes from the start of the experiment. During this period, water accumulation in the tubing was prevented by gravitational drainage back into the nebulizer. In addition, the O_2 concentration was constantly monitored with an O_2 analyzer.

Three different groups of experiments were conducted with the TR heaters with the thermostatic control adjusted to 3 different settings: coldest, warmest, and median. Results were recorded and tabulated for each unit studied and with different thermostat settings (table).

RESULTS

As anticipated, the temperature of the gases from water bath to the patient end T-piece adaptor showed a gradual reduction. Whereas the inspired air temperatures were consistent and higher than desirable while using the FT model heater humidifiers

*B & F Medical Products.

†Hudson model 1077.

‡Bennett model 0880.

§Yellow Springs Instrument Company model 47.

TABLE

Results of Inhalation System Temperature Observations Using Puritan FT and TR Model Immersion Heater Humidifiers in the Experimental System—All Observations Room Temperature 25.6° C, Relative Humidity 45%

Immersion heater model and thermostat setting	Temperature recording sites of system			
	Water in bath, °C Mean ± SD	Nebulizer outlet, °C Mean ± SD	Middle of tubing, °C Mean ± SD	T-piece adapter (inspired air), °C Mean ± SD
FT	58 ± 5	44 ± 2	39.6 ± 3	37.7 ± 3
TR—coldest	46 ± 15	36 ± 9	32 ± 8	30.5 ± 7.6
TR—warmest	64 ± 3	48 ± 2	43 ± 1	40 ± 1
TR—median	56 ± 8	43 ± 6	38.5 ± 5	35 ± 4.5

and the TR model with thermostat at the warmest possible setting, the TR models did not produce consistent values with lower settings of the thermostat.

Furthermore, the water temperature in the nebulizer peaked in 10 to 15 minutes; thereafter it remained steady as long as the water level remained within the "fill-to-level" and "refill" lines. With the nebulizer set for air dilution of 40%, the O_2 concentration recorded at the nebulizer outlet varied from 41 to 44%. It was also noted that if water was allowed to condense and accumulate in the aerosol tube without provision for gravitational drainage back into the nebulizer, the amount varied from 23 to 57 ml in 1 hour, depending on the temperature of the water in the nebulizer.

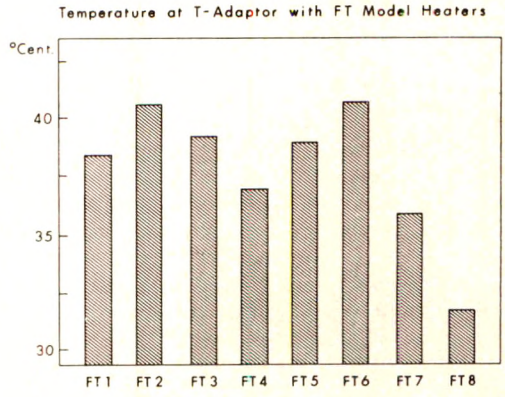


FIG 2. Temperature recorded at patient end T-adaptor with 8 FT model heaters.

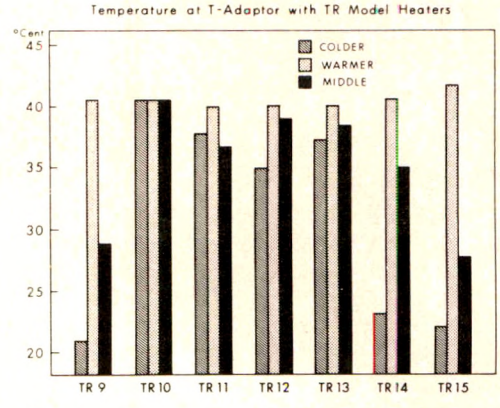


FIG 3. Temperature recorded at patient end T-adaptor with TR model heaters at 3 different thermostat settings.

DISCUSSION

Heated humidifiers raise the temperature of the water and are supposed to maintain it well above body temperature, to ensure that the gases passing downstream have temperatures around 37° C when they reach the trachea. This allows a considerable amount of heat and water to be administered to the patient. How well the tracheal mucosa tolerates heat is not well defined; prolonged breathing of air and O_2 at 37° C has been known to cause hyperpyrexia.[6] Hyperthermia has been reported in patients receiving IPPB using ventilators with heated humidifiers in the system where the temperature of inspired air varied from 29.4° to 41.7° C.[7]

Ideally, patients' air passages should not be exposed to temperatures above normal body temperature for long, since there are known deleterious effects on ciliary activity and possible direct thermal damage to the respiratory mucosa, but no harm should result if temperature of the inspired gases is maintained at 32° C. Air at this temperature, when 100% saturated, has a water content of 34 mg/L as compared to 44 mg/L in air at 37° C, a difference of only 10 mg. Preferably, the inspired air temperature should be monitored as close to the patient as possible. The Bennett MA-1 ventilator patient circuit incorporates an efficient cascade type thermostatically adjustable humidifier[8] with provision for monitoring the temperature of inspired gases downstream but, for practical reasons, not at the endotracheal connector.

Under clinically simulated conditions, except for the patient breathing air into the expiratory limb of the system, one finds that FT models performed more consistently, though in the majority of instances the inhaled air temperatures were higher than desired (fig 2). Thermostat settings were unreliable in most of the TR immersion heaters, which generally produced elevated inspired air temperatures with higher settings of the thermostat and were inconsistent with lower settings (fig 3).

Apparently the temperature of a heated aerosol reaching the patient in a system such as the one described depends on the following:

1. Type of breathing system—tracheostomy cannulas, endotracheal tubes, face masks, hoods, tents, etc.

2. The flow rate of gases.

3. The length, size, and thermal conductivity of aerosol delivery tubing.

4. The gradient between the heater and the ambient temperatures.

5. The level of liquid in the nebulizer container and rate of aerosol production.

The reliability and efficiency of the thermostat depends on its age, maintenance, cleaning, and sterilization. Sharp taps to the unit or dropping it on the floor can damage the thermostat. The greatest danger in the use of heated humidifiers is the possibility of thermostat failure and inhalation of excessively warm steam. If water is allowed to condense in the tubing and drain into the trachea instead of back into the humidifier, serious thermal damage to respiratory tract is possible.

An alternative to reduce excessive temperatures of the aerosol delivered to the patient is to elongate the aerosol tubing (in excess of 5 feet), though this becomes cumbersome, impractical, and wasteful. It is therefore recommended that close vigilance be kept over the actual temperature of the gases inhaled by patients.

In the above, we have studied the effects of 2 types of heater humidifiers on inspired air temperature with the air entrainment control for 40% O_2 only, since this is the commonly used level. The entrained room air at 40% O_2 setting might be expected to cool the aerosol mixture to a level below what might be expected with higher O_2 settings of 70 and 100%, since the proportion of entrained room air is less in these instances. These observations, with evaluation of some of the new units, will follow.

REFERENCES

1. Robinson JS: Humidification, Scientific Foundations of Anaesthesia. Second edition. Edited by D Scurr, S Feldman. London, Heinemann, 1974, pp 488-496

2. Bendixen HH, Egbert LD, Hedley-Whyte J, et al: Respiratory Care. St. Louis, The CV Mosby Company, 1965, pp 104-108

3. Egan DF: Fundamentals of Respiratory Therapy. Second edition. St. Louis, The CV Mosby Company, 1973, pp 194-247

4. Humidification (editorial). Lancet 2:344-345, 1956

5. Sara C: The management of patients with a tracheostomy. Med J Aust 1:99-103, 1965

6. Morgan JG: Problems of humidification, Modern Trends in Anaesthesia. Edited by T Evans, TC Gray. New York, Appleton-Century-Crofts, 1967, 3:242-255

7. Kirch TJ, DeKornfeld J: An unexpected complication (hyperthermia) while using the Emerson postoperative ventilator. Anesthesiology 28: 1106-1107, 1967

8. Wynands JE, Wrigley FRH: A simple method of humidifying gases. Can Anaesth Soc J 13:403-405, 1966

Clinical Investigation of a New Intravenous Anesthetic—Etoxadrol Hydrochloride (CL-1848C; U-37862A)

E. L. FREDERICKSON, MD*
DAVID E. LONGNECKER, MD†
GARY W. ALLEN, MD‡

Twenty-eight patients were anesthetized with etoxadrol as primary agent. The anesthesia produced was characterized by profound analgesia and amnesia, while pharyngeal and laryngeal reflexes, as well as swallowing and lid reflexes, remained active. Systolic, diastolic, and pulse pressure were slightly increased, with associated tachycardia and tachypnea. A dose of 0.75 mg/kg produced anesthesia for an average of 26 (14 to 53) minutes. Alternating nystagmus was present for several hours and associated with dreams and/or visions that were pleasing to most patients. Six patients, however, had unpleasant dreams for up to 24 hours. One patient given an excessive dose (4.65 mg/kg) was cataleptic, amnesic, and analgesic for 6 days. The occurrence of unpleasant dreams and aberrations in over 20% of the patients suggests that the drug probably has little usefulness in anesthesia. However, the extreme safety of the drug (an LD_{50} equal to some 20 to 40 times the ED_{50}) and the prolonged analgesia justified clinical testing. There was no evidence of metabolic or systemic organ system change from any of the clinical laboratory studies.

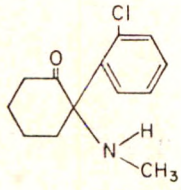
ETOXADROL hydrochloride, a newly developed anesthetic agent, has been found in animals to produce a state similar to that produced by ketamine but lasting 2 to 3 times longer. The compound is related to dexoxadrol, studied as an analgesic agent and with a potency similar to that of aspirin. However, analgesic doses of dexoxadrol produced mental confusion, hallucinations, and numbness of the arms and legs.[1] In etoxadrol, a much more potent agent than dexoxadrol, a phenyl group is replaced by an ethyl radical (figure). Chemically, it is unrelated to ketamine and other phencyclidine derivatives.

Extensive animal studies by Wilson and associates,[2-4] and by Hidalgo's group[5] have demonstrated that low doses of etoxadrol produce increased cardiac output with increased systolic, diastolic, and pulse pressures, associated with tachycardia, nystagmus, and salivation. The LD_{50} in many species was found to be 20 to 40 times the clinically effective dose. In monkeys, 2.5 mg/kg produced anesthesia adequate for endotracheal intubation and laparotomy, the anesthetic state usually lasting 25 to 30 minutes. The righting reflex was lost for an additional 90 minutes after the animal was returned to the cage.[5]

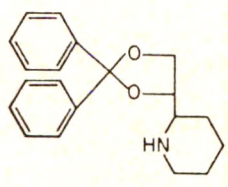
On the basis of prior work, Wilson's group[6] studied the drug in 13 healthy volunteers, reporting that a dose of 0.75 mg/kg produced a useful comatose state for 50 to

*Professor, Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia 30322.
†Associate Professor, Department of Anesthesiology, University of Virginia School of Medicine, Charlottesville, Virginia.
‡Anesthesiologist, Temple, Texas.

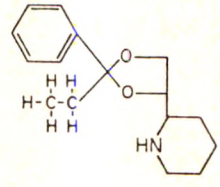
This study was supported in part by grants from Cutter Laboratories, Berkeley, California and from the Upjohn Company, Kalamazoo, Michigan.
Paper received: 8/6/75
Accepted for publication: 9/16/75



Ketamine



Dexoxadrol



Etoxadrol

FIGURE. Chemical structure of ketamine, dexoxadrol, and etoxadrol.

85 minutes in the 11 subjects given this dosage. A period of profound analgesia exceeded the period described as useful coma by varying amounts but was present in all subjects up to 2 hours or more. Each of the subjects experienced a major dream that seemed exceptionally real, the majority being described as pleasant or unusual experiences. In only one subject was there any evidence of a frightening situation; this occurred during the emergence phase and was thought by the investigators to be a "panic reaction." The EEG recorded from these subjects did not resemble that recorded during the use of any other drug, being characterized by an increase in the amplitude of an alpha activity, described as "juvenile alpha rhythm."

METHODS AND MATERIALS

The foregoing phase-I study in a comprehensive multidisciplinary, multiorgan evaluation of etoxadrol in normal human volunteers demonstrated the physiologic safety of this drug. We therefore decided to test etoxadrol in the clinical situation. After informed consent was obtained, the drug was administered to 14 patients by a single investigator. This initial clinical trial was later expanded to involve an additional 14 patients (table 1), using a similar clinical protocol.

RESULTS

The first 14 patients, anesthetized by one of us (ELF), underwent operations that were superficial in 6, urologic in 4, gynecologic in 2, orthopedic in 1, and thoracic in 1 (table 2). The anesthetic state produced by the drug was useful, and amnesia was complete for each patient. Relaxation was not good, and patients frequently made random movements of all their extremities, but the operative field remained quiet.

Induction doses ranged from 0.75 to 1 mg/kg IV over 20 to 40 seconds. Of the first 14 patients, only 2 stated they would not like to again have the same anesthetic for the same procedure, both complaining that the drug effect lasted too long, and one disliked the unpleasant dreams. Three of the 14 patients did not remember having

TABLE 1
Age and Sex of Patients

	20-40	40-60	>60	Total
Male	11 (4)	7 (5)	2 (1)	20 (10)
Female	1 (1)	5 (2)	2 (1)	8 (4)

(—)—Number of patients in original study.

TABLE 2
Surgical Procedures Performed with Etoxadrol Anesthesia

	Number of patients	Supplemental anesthesia
Superficial (skin grafts, burn dressings, excisions, biopsies, etc.)	12 (6)	6* (1)
Orthopedic	8 (1)	4 (1)
Urologic (cystoscopy or transurethral resections)	4 (4)	1 (1)
Dilation and curretage (with conization of cervix or radium insertion)	3 (2)	2 (2)
Thoracotomy with lobectomy	1 (1)	1 (1)
Totals	28 (14)	14 (6)

(—)—Number of patients in original study of 14.

*Three of these patients required supplemental anesthesia before surgery could begin.

TABLE 3
Premedications Used with Etoxadrol

None	2 (2)
Atropine or scopolamine	5 (1)
Morphine and atropine or scopolamine	8 (1)
Barbiturate and atropine or scopolamine	5 (4)
Barbiturate, narcotic, and atropine or scopolamine	3 (2)
Droperidol and scopolamine	2 (1)
Droperidol	1 (1)
Barbiturate and diazepam	1 (1)
Barbiturate, diazepam, and scopolamine	1 (1)
Total	28 (14)

(—)—Number of patients in original study.

dreams; however, 2 of these patients obviously had been dreaming in the postoperative state, so perhaps their recall inability was related to poor communications. The rest of the patients had dreams that were recalled as pleasant, although frequently described as unusual. The most impressive characteristic of this drug was prolonged profound analgesia.

On the basis of this experience, the study was enlarged to a multiinstitutional study involving 4 other investigators. The protocol was defined in a more rigid manner, but still the investigator was given leeway to treat any complications that might occur and to give dosage up to a maximum of 1.5 mg/kg and other anesthetic agents if required for anesthesia. Premedication varied according to the individual preference of each investigator (table 3). No significant difference was noted in regard to drug interaction with any of the premedicants used.

The majority of surgical procedures were primarily superficial, but a considerable number were orthopedic, believed to entail significant postoperative pain. The drug was used only as an induction agent for the thoracotomy. It was noted that less etoxadrol was required in elderly patients, and that the degree of relaxation obtained was much greater than in younger patients.

Although there was a great deal of variation between patients in the depth and duration of anesthesia, there was a characteristic response to the induction dose, commonly 0.75 mg/kg, but on 4 occasions, 1 mg/kg was used electively. Three patients required 1.125 mg/kg before there was sufficient quietude to begin the operation (table 4). The response to this induction dose was initially sluggish speech and a blank stare with alternating horizontal and vertical nystagmus. Several patients stated that their body felt numb and that they felt as though they were dying. Facial motions, commonly of the lips and the tongue, were frequently associated with a slow rolling motion of the head. Vocalization continued during the procedure in 6/28 patients. Surgical stimulation did not appear to modify what appeared to be verbalization of dreams.

Respiratory rate was invariably increased, but on 2 occasions, a period of apnea that lasted approximately 10 seconds preceded the onset of tachypnea. The cardiovascular system appeared to be receiving increased sympathetic stimulation, as demonstrated by the increase in systolic, diastolic, and pulse pressures. Heart rate also increased, but not to an alarming degree. One patient had premature ventricular contractions with bigeminy, lasting for approximately 60 seconds. This was associated with surgical stimulation of the lower urinary tract. All patients appeared warm and none perspired, even when responding to surgical stimulation.

Conversation with the patients was frequently possible, although their speech was slow and anything beyond a single-word

TABLE 4
Duration of Anesthetic Action
Mean Anesthesia Time in Minutes

	Total dose, mg/kg							
	0.75	1.0	1.125	1.25	1.5	2.0	2.5	4.65
Etoxadrol alone	26 (5)	44 (6)	—	—	101 (2)	—	—	104 (1)
Etoxadrol supplemented*	68 (3)	45 (1)	51 (3)	63 (1)	90 (4)	103 (1)	80 (1)	—

(—)—Indicates number of patients.

*Anesthesia time due only to etoxadrol could not be determined because other anesthesia (usually N_2O) was administered electively from the beginning of the procedure.

answer appeared difficult. Muscle relaxation was evident only in the elderly patients, and more characteristic was a plasticity of the limbs with mild catatonic positioning. Airway maintenance was never a problem unless salivation was excessive. Swallowing was not uncommon during the course of the procedure. Elderly patients frequently had a relaxed airway and required some airway support shortly after induction.

In 9 patients whose temperature was monitored continually during the operative and postoperative periods, the increase in temperature never exceeded 1° C, but more significantly, there was no decrease in temperature greater than 1° C. This was deemed unusual, especially in light of the usual hypothermic response in patients having burn dressing changes and skin grafts.

It was impossible to prevent movement in 3 patients, even though the recommended maximum dose of the drug was given. For these procedures, the drug was considered unsatisfactory and other anesthetics were administered. All three of these patients were in the superficial surgery group and in the latter group of 14 patients. One had received morphine and atropine for premedication five hours before induction (case delayed) and scopolamine 0.2 mg IV seven minutes before induction. The other two received only atropine for premedication. Supplemental nitrous oxide only was needed for these last two patients for completion of their burn dressing change, but the former required morphine 4.0 mg IV as well as nitrous oxide so his ulnar neurolysis could be completed. The other 11 patients received nitrous oxide electively at the beginning of the procedure or because the maximum dose of etoxadrol had been used and a greater amount of anesthesia time was needed.

Adverse or threatening dreams were reported by 6/28 patients, all of whom had a prolonged period of recovery. Of these, 3 recalled periods of psychotic activity when they were totally unable to control their thoughts or actions. Only 7/28 patients stated that they had no dreams, and the dream content of the others most commonly included comments such as "floating," "puffy," and "out of this world." Relationship of dream content to past events in the patient's life was common. An individual who had been wounded in Vietnam had dreams of this unpleasant event. In contrast, most of the dreams were pleasant, relating to such things as childhood, trips away from home, military duty in Japan, or frequently just association with a pleasant scene.

Such mental aberrations frequently persisted up to 18 to 24 hours. However, they were voluntarily controlled by most of the patients and could be reinstituted if the patient closed his eyes. In one patient (who had inadvertently been given 4.65 mg/kg) this effect lasted for 6 days.

One of the most profound results of etoxadrol was the production of an analgesic state characterized by an awareness of pain when called to the patient's attention, but frequently accompanied by the statement "It doesn't bother me." Postoperative analgesic agents were rarely needed, and stimulation of donor sites of skin graft elicited little or no response, even though the patient was responding rationally.

Of the 28 patients, 5 vomited without nausea following postoperative fluid intake. One patient, who had a previous history of nausea and vomiting after other anesthetic procedures, continued with nausea and vomiting for 48 hours after anesthesia with this drug.

Postoperative clinical laboratory studies showed no significant changes in hemoglobin, red or white blood count, hematocrit, creatinine, urinalysis, SGOT, LDH, alkaline phosphatase, or total blood proteins. Two of the patients had mildly elevated BUN, both before and after operation, and 4 had a minimally elevated SGOT, both before and after operation.

DISCUSSION

As the response pattern to etoxadrol is new to anesthesia, comparison in this study is primarily based on subjective comments and opinions of the clinical response of patients. The drug does produce a comatose state characterized by CNS, cardiovascular, and respiratory stimulation.

In attempting to group this compound with other anesthetic agents, we are obliged to compare it with the group classified by Winters and associates[7] as demonstrating all states of electrical activity in the EEG up to generalized seizures. This group includes the phencyclidine compounds, gamma hydroxybutyrate, alpha chloralose, trichloroethylene, and enflurane, a variety of compounds that appear to have no chemical relationship. However, they all produce a state of CNS depression and analgesia frequently associated with hallucinatory and

epileptoid components in primates, including man. Chen[8] states that the arylcycloalkylamines (phencyclidine, cyclohexamine, and ketamine) and the 1,3 dioxolanes (dexoxadrol and etoxadrol) are "sympathomimetic anesthetics," classified as anesthetic agents only because they eliminate the response to surgical stimuli in a reversible manner. The obvious lack of inhibition, EEG changes, and behavioral changes seen in animals, as well as the production of profound analgesia, imply that the action of these drugs on the CNS is widely ramified, either by direct action on receptor sites or indirectly by modification of neurotransmitter synthesis, metabolism, release, or uptake.

Future study of these drugs may elucidate the mechanism of CNS changes. Current studies on various monoamines within the CNS demonstrate that profound behavioral effects and sleep are produced by changes in both content and turnover rate of these amines. It is evident from these and other studies that serotonin, norepinephrine, and dopamine are all of significance in terms of CNS function.[9]

We have found a significant difference in brain concentration of these amines during and after the administration of thiopental, ketamine, and etoxadrol. The apparent rate of synthesis of brain serotonin was reduced to 50 to 60% of control levels 4 hours after administration of both ketamine and etoxadrol. These drugs also produced increases in the apparent rate of brain dopamine synthesis, which reached as much as 200% of control 6 hours after administration. In contrast to this, thiopental caused only a marginal decrease in the apparent synthesis rate of brain serotonin and a 30% decrease in apparent synthesis rate of dopamine in rats.[10]

The production and incidence of dreams during or after anesthesia, characteristic of many anesthetic agents, has received the attention of many investigators, especially with ketamine.[11] Brice and colleagues[12] and Crawford's group[13] demonstrated a high incidence of dreaming during thiopental-N_2O-relaxant anesthesia. The mental aberrations observed in our study do not necessarily relate to awareness during operation, although the surgical procedure may stimulate the delusion. One of our patients had a lymph node removed from the anterior cervical chain just cephalad to the thyroid gland. After recovery, he claimed he had watched the operation from a corner of the operating room, finding it not an unpleasant experience. Memory of actual events during the surgical procedure could not be elicited from any of our patients.

The high incidence of unpleasant dreams or psychotic experience has prevented further clinical investigation of etoxadrol as an anesthetic agent. However, continued animal studies relating to both its analgesic action and CNS effects have continued.[14] It is hoped that future studies will further our understanding of the mechanism of action of anesthetic agents and of analgesia, for the increased safety and efficacy of anesthesia.

REFERENCES

1. Lasagna L, Pearson JW: Analgesic and psychotomimetic properties of dexoxadrol. Proc Soc Exp Biol Med 118:352-354, 1965

2. Wilson RD, Traber DL: The effect of hexamethonium on the pressor response to CL-1848C, a new dissociative anesthetic. Pharmacologist 11:236, 1969

3. Traber DL, Priano LL, Wilson RD: Effects of CL-1848C, a new dissociative anesthetic on the cardiovascular and respiratory system. J Pharmacol Exp Ther 175:395-403, 1970

4. Kelly RW, Wilson RD, Traber DL, et al: Effects of two new dissociative anesthetic agents, ketamine and CL-1848C, on the respiratory response to carbon dioxide. Anesth & Analg 50:262-269, 1971

5. Hidalgo J, Dileo RM, Rikimaru MT, et al: Etoxadrol (CL-1848C) a new dissociative anesthetic: studies in primates and other species. Anesth & Analg 50:231-239, 1971

6. Wilson RD, Traber DL, Barratt E, et al: Evaluation of CL-1848C: a new dissociative anesthetic in normal human volunteers. Anesth & Analg 49:236-241, 1970

7. Winters WD, Mori K, Spooner CE, et al: The neurophysiology of anesthesia. Anesthesiology 28: 65-80, 1967

8. Chen G: Sympathomimetic anaesthetics. Can Anaesth Soc J 20:180-185, 1973

9. Weiss B, Laties VG: Behavioral pharmacology and toxicology. Ann Rev Pharmacol 9:297-326, 1969

10. Sung YF, Frederickson EL, Holtzman SG: Effects of intravenous anesthetics on brain monoamines in the rat. Anesthesiology 39:478-487, 1973

11. Garfield JM, Garfield FB, Stone JG, et al: A comparison of psychologic responses to ketamine and thiopental - nitrous oxide - halothane anesthesia. Anesthesiology 36:329-338, 1972

12. Brice DD, Hetherington RR, Utting JE: A simple study of awareness and dreaming during anaesthesia. Br J Anaesth 42:535-542, 1970

13. Crawford JS, Harley NF, Bland EP, et al: Awareness under anaesthesia. Br Med J 1:508, 1969

14. Tang AH, Kirch JD: Analgetic activities of etoxadrol in the rhesus monkey and in mice. Anesth & Analg 52:577-583, 1973

Endobronchial Intubation for Intraoperative Protection of a Single Functioning Lung: A Case Report

JAY B. BRODSKY, MD*
MICHAEL D. ABRAMAWITZ, MB†
MARY P. MEHREZ, MD‡

ELECTIVE endobronchial intubation is usual for intrathoracic surgery. A case is presented demonstrating a role for endobronchial anesthesia in situations when assured access to a single lung is necessary.

A 51-year-old woman was admitted with signs and symptoms of acute spinal-cord compression. Five months earlier, carcinoma of the right lung with lymph-node involvement had been diagnosed, for which she was treated with radiation (6000 r) to the trachea, carina, and paratracheal lymph nodes. In the 2 months before admission, the patient experienced increasing thoracic back pain associated with dyspnea, developed a productive cough, and was given antibiotics for multiple right-lung abscesses noted on chest x-ray.

On admission, gas myelography demonstrated collapse and destruction of the 6th thoracic vertebral body, associated with an epidural soft-tissue mass which compressed the spinal cord. Emergency decompressive surgery was indicated. A preoperative roentgenogram showed a large, left paratracheal lymph node compressing the trachea, and a completely opaque right hemithorax. Breath sounds were absent on the right but the left lung was clear.

An arterial blood-gas sample, drawn while the patient breathed room air, showed Pao_2 71 torr, $Paco_2$ 32 torr, pH 7.47, total CO_2 23 mM/L, and base excess +1 mEq/L. Thoracocentesis yielded 500 ml of serosanguinous fluid, but the procedure was discontinued when the patient experienced pleuritic pain. Postthoracocentesis chest x-ray showed no reduction in the right pleural effusion or reexpansion of the collapsed right lung (fig 1).

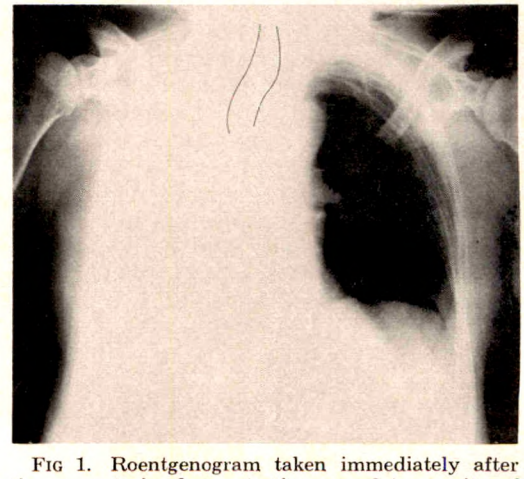


FIG 1. Roentgenogram taken immediately after thoracocentesis, demonstrating complete opacity of right lung. Dark lines outline position of trachea as determined by bright-light transillumination of original x-ray.

*Anesthesiologist, Letterman Army Medical Center, San Francisco.

†Resident, Beth Israel Hospital, Boston.

‡Anesthesiologist, Beth Israel Hospital, Boston.

The opinions and assertations contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Reprint requests should be addressed to Technical Publications Editor, Letterman Army Medical Center, Presidio of San Francisco, California 94129.

Paper received: 4/28/75
Accepted for publication: 10/22/75

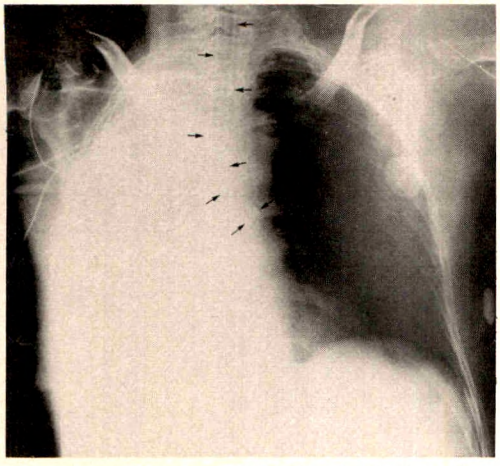


FIG 2. Roentgenogram following intubation, demonstrating (arrows) that left endobronchial tube has bypassed site of potential obstruction, permitting patient to be placed prone. Note also some aeration of right lung, due to positive-pressure ventilation.

Anesthetic induction consisted of preoxygenation, followed by a sleep dose of sodium thiopental, d-tubocurarine to prevent fasciculations, and succinylcholine to facilitate intubation. The larynx was sprayed with 4% lidocaine, and a 35-French Carlens left double-lumen endobronchial tube was passed (fig 2).

The patient, placed in the prone position, underwent a 2-hour decompressive thoracic (T5-7) laminectomy under N_2O-O_2-halothane anesthesia, with increments of d-tubocurarine, without complications. Ventilation was controlled and intraoperative blood-gas samples demonstrated satisfactory gas exchange.

After postoperative return to the supine position, the patient received atropine and neostigmine and was extubated in the operating room. In the recovery room, she breathed 40% O_2 via a heated nebulizer without respiratory difficulty and was returned to her room 4 hours postoperatively.

The patient's immediate postoperative course was satisfactory and she showed signs of neurologic improvement, but the right pleural effusion persisted and required frequent drainage. Eventually nitrogen mustard successfully prevented reaccumulation of the effusion, and the right lung was partially reexpanded. However, the patient developed antibiotic-resistant pneumonia and expired 7 weeks postoperatively from respiratory failure.

DISCUSSION

In 1931, Gale and Waters[1] suggested the use of single-lumen cuffed tubes for closed endobronchial anesthesia during thoracic surgery. Carlens,[2] in 1949, introduced the double-lumen endobronchial catheter into clinical practice. These technics are usually employed to prevent contralateral spread of material from diseased to healthy lungs and to provide a selectively collapsed lung when necessary during intrathoracic surgery.[3-5]

Our patient had a single functioning lung. The potential hazard of obstruction of the main bronchus to that lung from extrinsic compression by enlarged paratracheal lymph nodes was revealed by the preoperative chest x-ray. Placing the patient prone for the surgical operation would have made access to her functioning left lung difficult in the event of intraoperative upper-airway obstruction. Elective endobronchial intubation bypassing the site of possible airway obstruction was demonstrated radiologically prior to turning the patient to the prone position.

In addition to assuring access to the left lung, the double-lumen Carlens tube isolated that lung from the secretions and tumor cells of the opposite lung. Any double-lumen left endobronchial tube would have been equally appropriate. Intraoperative ventilation of both lungs demonstrated some aeration of the right lung during controlled positive-pressure ventilation (fig 2).

Intraoperative endobronchial intubation should be considered in emergency operations with potential compromise of a single functioning lung, although this technic is not without hazards, since trauma to the airway from difficult intubation can potentiate obstruction, especially during the immediate postextubation period. Patients should be carefully observed in the recovery room or intensive care unit following extubation, and means for establishing an open airway should be available by the bedside.

ACKNOWLEDGMENT

The patient's case record is filed at Beth Israel Hospital, Boston.

REFERENCES

1. Gale JW, Waters RM: Closed endobronchial anesthesia in thoracic surgery. J Thorac Surg 1: 432-437, 1931-32

2. Carlens E: A new flexible double-lumen catheter for bronchospirometry. J Thorac Surg 18:742-746, 1949

3. Moody JD: Endobronchial occlusion during pulmonary resection. J Thorac Surg 18:82-89, 1948

4. Ruth HS, Grove DD, Keown KK: Endobronchial anesthesia by means of an improved endobronchial airway. Anesthesiology 9:422-429, 1948

5. Björk VO, Carlens E: The prevention of spread during pulmonary resection by the use of a double-lumen catheter. J Thorac Surg 20:151-157, 1950

THE EFFECT OF PROLONGED BREATHING OF O_2 IN HIGH CONCENTRATION ON THE RESPIRATORY SYSTEM: EXPERIMENTAL INVESTIGATIONS. Although no attempt was made to extrapolate results from dogs to man, statistically impressive data were derived from a study of 17 dogs (7.5 to 30 kg) investigated to answer 3 major questions: (1) What is the effect (in dogs) of breathing 100% O_2 at 1 atm (600 torr) for up to 48 hours? (2) Can controlled respiration alter the action of prolonged O_2 breathing in high concentrations? (3) What, if any, pulmonary damage results from breathing? Assessment of the cardiorespiratory system was based on an analysis of indices determining (1) respiratory mechanics, (2) ventilation:perfusion relationships, (3) gas-exchange values, (4) O_2 transport and utilization in tissues, (5) morphologic lung changes. The author concludes: (1) All dogs showed pulmonary damage after 30 hours, changes beginning by the 12th hour and appearing during spontaneous as well as mechanical O_2 ventilation. (2) Respiratory rate, A: a ratio, and pulmonary shunting increased; lung compliance decreased; CO_2 excretion was impaired. (3) Pulmonary morphology showed extensive atelectasis and exudative reaction. (4) Mechanical respiration increased the O_2-induced damage. (5) Long-term quiet breathing of O_2 also disturbed the $\dot{V}/\dot{Q}$ ratio. (6) If long-term high concentrations of O_2 must be administered, Pa_{O_2} should not be permitted to exceed 100 torr, as dysplasia bronchopulmonalis is likely to result even earlier in man than in dogs. *(Szreter. Anaesth Resusc Intensive Ther 1:305-324, 1973.)*

Prolonged Neuromuscular Blockade with Pancuronium in the Presence of Acute Renal Failure: A Case Report

DWIGHT G. GEHA, MD*
CASEY D. BLITT, MD†
B. J. MOON, MD‡
Tucson, Arizona§

Prolongation of neuromuscular block following pancuronium administration to anephric patients has been reported. A patient is described whose postoperative course after resection of gangrenous bowel was complicated by acute renal failure and prolonged neuromuscular blockade. A large intraoperative dose of pancuronium was administered without monitoring neuromuscular transmission with a peripheral nerve stimulator.

The course was further complicated by administration of gentamicin, an antibiotic known to potentiate neuromuscular blocking drugs. Complete return of neuromuscular transmission occurred 60 hours after administration of the last dose of pancuronium and subsequent to peritoneal dialysis.

After rapid distribution from plasma, pancuronium, like curare, is eliminated by the renal pathway. The absence of renal excretion considerably increases the duration of action of curare when given in high doses. It has been suggested that doses of pancuronium greater than 3.6 mg/sq m or multiple doses would result in prolonged neuromuscular block in patients without renal function. The case reported illustrates the importance of monitoring neuromuscular transmission during administration of pancuronium in the presence of renal insufficiency to avoid this complication.

PROLONGED neuromuscular blockade following pancuronium administration has been reported (1) in a healthy young woman,[1] (2) in association with the antibiotic polymyxin-B,[2] and (3) in an anephric patient with biliary obstruction and evidence of hepatocellular dysfunction.[3] Adler and Pilon[4] found that anephric cats required twice as long as normal animals for return of neuromuscular transmission following pancuronium. In a clinical study, Miller's group[5] found that single doses of 1.8 to 5.5 mg of pancuronium given to patients in renal failure resulted in a neuromuscular block lasting 20 to 40 minutes longer than in patients with normal renal function.

This report describes a patient who received a large intraoperative dose (11.8 mg/sq m body surface area) of pancuronium and whose subsequent postoperative course was complicated by acute renal failure and prolonged neuromuscular blockade. In addition, the patient received 2 doses of gentamicin, an antibiotic known to be associated with clinical neuromuscular block.[6,7] Of major importance, however, was the failure to monitor neuromuscular transmission

*Assistant Professor.
†Assistant Professor.
‡Resident.
§Department of Anesthesiology, University of Arizona College of Medicine, Tucson, Arizona 85724.
Reprint requests to Dr. Blitt.
Paper received: 7/14/75
Accepted for publication: 10/24/75

with a peripheral nerve stimulator. If the dose of pancuronium had been "titrated" according to the twitch response, an excessive dose would not have been given.

CASE REPORT

A 63-year-old Caucasian woman was admitted to the emergency room comatose, dyspneic, cyanotic, and in shock. Systolic blood pressure was 70 torr, heart rate 120 bpm, and rectal temperature 39.6 C. The abdomen was markedly distended. Initial resuscitative efforts included administration of O_2, 2 L of balanced salt solution, dopamine by continuous infusion, hydrocortisone sodium succinate (1 gm), gentamicin (80 mg), sodium cephalothin (2 gm), and digitalis.

History revealed 48 hours of nausea, vomiting, abdominal pain, intermittent hematochezia, several diarrheal stools, and absence of urination. Past history included cobalt irradiation for a transitional-cell carcinoma of the bladder 2 years previously. An intravenous pyelogram at that time indicated a nonfunctioning right kidney. In addition, she had a history of asthma treated with 40 units of ACTH monthly and self-administered aminophylline.

Despite initial improvement, the patient became increasingly tachypneic. The trachea was intubated and mechanical ventilation instituted. Pancuronium bromide (6 mg) IV was given to achieve a satisfactory ventilatory pattern and an acceptable peak inspiratory pressure. A diagnosis of septic shock due to large-bowel obstruction and necrosis was made and the patient was taken to the operating room.

Anesthesia was induced and maintained with N_2O-O_2 and fentanyl. At the time of induction, gross movements indicated recovery from the previous neuromuscular blockade, and pancuronium (4 mg) was given. Fentanyl (0.25 mg) and additional pancuronium (14 mg) were administered during a 6-hour surgical procedure consisting of lysis of adhesions, colon resection, and colostomy. The total dose of pancuronium, including the 6 mg given preoperatively, was 24 mg. No peripheral-nerve stimulator was used. Fluids administered totaled 5500 ml of crystalloid, and urine output was 320 ml. At the conclusion of the operative procedure, the patient was taken to the ICU with the endotracheal tube in place and mechanically ventilated with a Bennet MA-I respirator. No attempt was made to antagonize the neuromuscular block. The patient was unresponsive, but vital signs were stable, with blood pressure 120/90 torr, heart rate 100 bpm, CVP 15 cm H_2O, and rectal temperature 36.6 C. Arterial blood-gas values on F_{IO_2} 0.5 showed a Pa_{O_2} of 96 torr, Pa_{CO_2} 33 torr, pH 7.40, and HCO_3 21 mEq/L. Total protein was 5.1 mg/100 ml with albumin of 2.7 mg/100 ml. During the first 3 postoperative days, electrolytes were Na^+ 142 to 148 mEq/L, Cl^- 92 to 100 mEq/L, K^+ 3.8 to 5.1 mEq/L, and CO_2 20 to 25 mEq/L. BUN increased from 50 mg/100 ml to 90 mg/100 ml and creatinine from 3 mg/100 ml to 7.6 mg/100 ml.

During the first 12 hours in the ICU, urine output remained low, totaling less than 600 ml, in spite of crystalloid fluids, 5% purified protein fraction (Plasmanate®), and repeated doses of furosemide (Lasix®). Serum and urine osmolality were 303 mOsm and 291 mOsm, respectively, and urine Na 51 mEq/L, compatible with acute renal failure. The patient continued to be unresponsive.

Fourteen hours after the last dose of pancuronium, and nearly 20 hours after the initial dose, a peripheral nerve stimulator (Burroughs-Wellcome, 50 Hz) applied in the area of the ulnar nerve at the wrist via subcutaneous needle electrodes elicited no twitch and no response to tetanic stimulation.

On the morning of the 2nd postoperative day and 37 hours after the last dose of pancuronium, a slight twitch, rapid fade in response to 50 Hz stimulation and post-tetanic facilitation were observed. Several hours later, the patient received a second dose of gentamicin (80 mg) IM and an hour later the twitch response was absent. Later in the afternoon, peritoneal dialysis was instituted, with 11 dialysis runs by the following morning. At that time, 60 hours after the last pancuronium dose, a strong twitch, sustained tetanus, and absence of post-tetanic facilitation were observed. The patient died on the 13th postoperative day from renal failure, gram-negative sepsis, and septic shock.

DISCUSSION

The cessation of effect of neuromuscular blocking drugs other than succinylcholine depends upon redistribution and excretion, mainly by urinary filtration.[8] Following IV administration, plasma concentration reaches an initial peak and then falls rapidly in

an exponential manner. Using isotope-labeled compounds, it has been shown that the drugs will be localized in muscle, especially concentrated at the junctional area, but the highest tissue concentrations are present in liver, spleen, and kidney.[8]

Recently, Gibaldi and coworkers[9] have described a pharmacokinetic, multicompartmental model for the distribution and elimination of d-tubocurarine (dTc) in man, based upon previously reported data on plasma and extracellular fluid. It further illustrates that there is a disproportionate increase in duration of effect of dTc with large doses. Using this model, Gibaldi's group have shown that absence of renal excretion increases the duration of action of curare only slightly in the low-dose range but considerably in the high-dose range.[10] They conclude that renal failure will primarily affect the duration of action of large single and multiple doses of d-tubocurarine.

The elimination of pancuronium in man has been reported by Agoston and associates.[11] A single IV injection of pancuronium disappears from plasma in 3 phases with a half-life of less than 5 minutes, 7 to 13 minutes, and 108 to 147 minutes, respectively. Detectable levels are still present after 4 hours. At 30 hours, approximately 40% of the injected dose was recovered in the urine and 10% in bile. A small amount of this was accounted for by 1 metabolite and the remainder was unchanged pancuronium. Thus it appears that the distribution and elimination of pancuronium and dTc are similar.

Miller's group[5] found that 1.8 to 5.5 mg of pancuronium resulted in a duration of neuromuscular block 20 to 40 minutes longer in anephric patients than in patients with normal renal function. Assuming that pancuronium is 5 to 8 times more potent than dTc, his results were comparable to those predicted by the computer model of Gibaldi for dTc in patients with renal failure. Based on this comparison, Miller suggested that doses of pancuronium greater than 3.6 mg/sq m or multiple doses would result in prolonged neuromuscular block in patients without renal function.

Renal excretion is the primary pathway of elimination of both dTc and pancuronium. In the absence of renal function, the biliary elimination of dTc is increased fourfold.[12] Whether this occurs with pancuronium is not known. Thus the dose of pancuronium administered in the presence of decreased or absent renal function must be carefully controlled, especially if more than 1 increment is given. The degree of neuromuscular block present and the amount of neuromuscular blocking-drug required can be adequately assessed only by a peripheral nerve stimulator.

REFERENCES

1. Belafsky MA, Klawans HL: Prolonged neuromuscular blockade with pancuronium bromide in a young healthy woman. Anesthesiology 40:295-296, 1974

2. Fogdall RP, Miller RD: Prolongation of a pancuronium-induced neuromuscular blockade by polymyxin-B. Anesthesiology 40:84-87, 1974

3. Abrams RE, Hornbein TF: Inability to reverse pancuronium blockade in a patient with renal failure and hepatic disease. Anesthesiology 42:362-364, 1975

4. Adler L, Pilon RD: The duration of neuromuscular blockade with pancuronium in anephric cats. Abstracts of Scientific Papers, American Society of Anesthesiologists Meeting, 1972, pp 169-170

5. Miller RD, Stevens WC, Way WL: The effect of renal failure and hyperkalemia on the duration of pancuronium neuromuscular blockade in man. Anesth & Analg 52:661-666, 1973

6. Pittinger C, Adamson R: Antibiotic blockade of neuromuscular function. Annu Rev Pharmacol 12:169-184, 1972

7. Warner WA, Sanders E: Neuromuscular blockade associated with gentamicin therapy. JAMA 215:1153-1154, 1971

8. Karis JH, Gissen AJ: Evaluation of new neuromuscular blocking agents. Anesthesiology 35: 149-157, 1971

9. Gibaldi M, Levy G, Hayton WF: Kinetics of the elimination and neuromuscular blocking effect of d-tubocurarine in man. Anesthesiology 36:213-218, 1972

10. Gibaldi M, Levy G, Hayton WF: Tubocurarine and renal failure. Br J Anaesth 44:163-165, 1972

11. Agoston S, Vermeer GA, Kersten UW, et al: The fate of pancuronium bromide in man. Acta Anaesthesiol Scand 17:267-275, 1973

12. Cohen EN, Brewer HW, Smith D: The metabolism and elimination of d-tubocurarine-H^3. Anesthesiology 28:309-317, 1967

Unrelenting Hypotension Associated with an Acute Abdomen in a Comatose Hemophiliac Child: A Case Report

ROBERT W. VAUGHAN, MD*
SUSAN L. WILSON, MD†
LAWRENCE S. WALDBAUM, MD‡
St. Louis, Missouri§

A comatose 4-year-old hemophiliac presented with an acute abdomen; subsequently he developed unrelenting hypotension. An immediate exploratory laparotomy was required, without time for determining baseline factor VIII (AHF) levels. Despite hypotension and hemorrhage, vigorous intraoperative fluid volume replacement and the administration of fresh frozen plasma and AHF concentrates brought a successful conclusion.

SUCCESSFUL operative management of hemophiliacs requires a team effort by anesthesiologist, surgeon, and hematologist. Pechet and Glaser[1] reviewed the problems encountered in the surgical treatment of such patients. Although preoperative assessment of factor-VIII (antihemophilic globulin, AHF) plasma levels is desirable to evaluate the efficacy of therapy,[2] one may be forced to proceed with anesthesia and operation without this initial laboratory guide. In such an emergency, readily available AHF concentrates and fresh frozen plasma are mandatory. This case report emphasizes numerous problems one can encounter in a hemophiliac presenting for emergency surgery.

REPORT OF A CASE

An obese 4-year-old Negro boy, weighing 29 kg, had been active until 5 days prior to admission, when he developed vomiting, frontal headache, and was treated at another hospital with IM penicillin. Past history was significant in that the patient was a hemophiliac, a diagnosis made at 8 months of age, when he suffered an intracranial hemorrhage. During that hospitalization, a ventriculoperitoneal (VP) shunt was made for communicating hydrocephalus. His progress over the ensuing 3½ years was marked by periodic emergency room and clinic visits for spontaneous bleeding episodes.

Four days before admission to our hospital, the frontal headaches progressed to grand mal seizures. His overall neurologic condition worsened, and he was transferred to our hospital. On admission to the pediatric service, his state of consciousness fluctuated between lethargy and combativeness. Although no history of trauma was obtainable, this possibility could not be excluded because of his disoriented, uncooperative mental status. Vital signs in the emergency room revealed a blood pressure of 70/40 torr, pulse rate between 170 to 200 bpm, and rectal temperature of 38.5 C.

Significant physical findings included marked abdominal distention, with a palpable left upper-quadrant mass, fullness of

*Associate Professor of Anesthesiology.
†Assistant Professor, Department of Anesthesiology, Wadsworth VA Hospital, Los Angeles, California.
‡Resident, Barnes Hospital.
§Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri 63110.
Reprint requests to: Dr. Robert Vaughan, Dept. of Anesthesia, Arizona Medical Center, Tuscon, AZ 85724.

Paper received: 6/6/75
Accepted for publication: 9/18/75

the right temporal area over the VP shunt, massive swelling of the right upper arm at the previous IM injection site with faintly perceptible distal pulses, and well-healed scars from 7 previous peripheral cutdowns. Pertinent abnormal laboratory findings included a hematocrit of 22%, serum K^+ 3 mEq/L, and chest radiograph revealing scattered peripheral infiltrates. Although a radiograph of the abdomen confirmed the huge abdominal mass, the position of the catheter tip for the VP shunt could not be definitively located.

The surgical service was consulted for placement of an IV cutdown in the left forearm; 200 ml of lactated Ringer's solution with 5% dextrose was given, leading to an increase in systolic pressure (110 torr). Nevertheless, while still in the emergency room, the patient became more lethargic, again developed hypotension (50 torr systolic), and suffered a respiratory arrest. A 4 mm ID uncuffed endotracheal tube was placed. Two units of non-type-specific O-negative packed erythrocytes were transfused, plus an additional 1000 ml of crystalloid solution (equally divided between normal saline [NS] and lactated Ringer's [RL]), without an increase in blood pressure. As the abdominal girth continued to increase, the carotid pulses became barely palpable. The patient was rapidly transferred to the operating room.

Upon presentation for immediate exploratory laparotomy, systolic blood pressure was 50 torr, carotid pulses (rate = 160 - 180) were faintly palpable, and breath sounds were absent to auscultation of the left hemithorax. The endotracheal tube was withdrawn until breath sounds were bilaterally equal; however, because of copious secretions and an inability to adequately suction through the small tube, optimal ventilation was impossible. A 5.5 mm ID uncuffed endotracheal tube was rapidly placed and its position verified by auscultation. Subsequently, copious amounts of brownish-yellow material could be suctioned from the airway.

While ventilation was controlled with 100% O_2, d-tubocurarine was given IV (1 mg increments) to produce muscle relaxation, with N_2O added to a maximum of 50% concentration for anesthesia. As long as blood and electrolyte fluids were continuously administered by syringe, the systolic blood pressure (using a cuff on the left leg) could be maintained at 50 to 60 torr. An unsuccessful attempt was made to place a Doppler probe near the popliteal artery. Neither upper extremity could be used for monitoring blood pressure.

Certainly, a central venous pressure (CVP) determination could have helped gauge the rate of fluid and blood administration. Several considerations made us reluctant to place this monitor. For example, the only route available for the catheter was a second left upper-extremity cutdown or percutaneous subclavian or internal jugular puncture. In this hemophiliac, the safety of both options seemed questionable. Furthermore, we were hesitant to rely on whatever reading we obtained without radiographic verification of catheter tip placement.

Accordingly, placement of a CVP monitor was deferred. Since the preoperative diagnosis was intraabdominal hemorrhage, the surgeons proceeded with an immediate exploratory laparotomy. Total fluid volume administered during the course of the unrelenting preoperative hypotension included 2 units each of whole blood, packed erythrocytes, fresh frozen plasma, and electrolyte fluids (RL and NS), and 3 ml/kg of AHF concentrate.

A transverse abdominal incision down to the peritoneum resulted in profuse venous bleeding. No free blood was visible through the peritoneum. All fluid and blood administration was discontinued. Only when the peritoneum was opened was the extent of the abdominal mass appreciated. It extended from behind the stomach into the left upper quadrant and almost filled the abdominal cavity. Marked venous engorgement was also demonstrable in the vessels of the lower abdomen. Bloody fluid (900 to 1200 ml) was drained from the cyst. Progressively, blood pressure rose from 60 torr systolic to 120/70 torr. Exploration of the abdomen revealed no other bleeding sites. The pancreatic pseudocyst was marsupialized to the posterior stomach wall and the abdomen was closed without incident.

Neuromuscular block was antagonized with the IV administration of neostigmine (0.07 mg/kg) while simultaneously blocking the muscarinic receptors with IV atropine (0.02 mg/kg). With endotracheal tube in place, the patient was transferred with continuous O_2 administration to the pediatric intensive care unit. Upon arrival, frothy pink fluid was suctioned from the airway. Hematocrit was 66%; chest radiograph

was consistent with the diagnosis of pulmonary edema, aspiration pneumonitis, and/or "shock lung." Subsequent therapy included controlled mechanical ventilation, phlebotomy (700 ml) to a hematocrit of 40%, and furosemide (1 mg/kg), repeated twice (1 hour apart). Mechanical ventilation was maintained for 48 hours; weaning and extubation were without incident. The remaining portion of the hospital course was uneventful, with factor-VIII levels maintained above 30% during the postoperative period.

DISCUSSION

This patient's persistent hypotension was treated vigorously with volume replacement. In face of an enlarging abdominal mass with hypotension in a hemophiliac, the most likely preoperative diagnoses were either a ruptured spleen with intraabdominal hemorrhage or bleeding from an intraabdominal complication of the VP shunt. Ideally, we would have awaited AHF levels before proceeding with operation. However, the patient's cardiovascular status forced operation without adequate preparation.

Iatrogenic fluid overload resulted from the mistaken assumption of intraabdominal blood loss. Nevertheless, in retrospect, the volume therapy seems appropriate in view of the hypotension associated with increasing abdominal girth. Cardiac filling depended upon our continuous fluid infusion by way of the superior vena cava; almost complete inferior vena cava obstruction prevented venous return. With surgical evacuation of the pancreatic pseudocyst, venous return from the inferior vena cava resumed and blood pressure promptly returned toward normal. With reentry of the administered volume into the effective circulating blood volume and discontinuance of controlled mechanical ventilation, pulmonary edema ensued.

Several possibilities exist to explain this edema. The most obvious is volume overload; however, underlying aspiration pneumonitis with damage to the alveolar epithelium could not be excluded. A significant probability exists that regurgitation with aspiration occurred before the patient's arrival in the operating room. Treatment of this possibility included controlled mechanical ventilation with supplemental O_2, but without corticosteroids or antibiotics. Tillotson and Finland[3] have shown that the prophylactic use of antibiotics following aspiration may be unwarranted, especially since resistant superinfection is likely after administration of antibacterial agents. Recently, Downs and associates[4] showed in dogs that the effects of hydrochloric acid-induced aspiration pneumonitis were unaltered by low, high, or multiple doses of methylprednisolone.

Malfunction of the venous portion of the VP shunt, with subsequent compression of the catheter tip, was judged responsible for the right temporal fullness causing increased intracranial pressure (ICP). Prior to admission, this led to fluctuating levels of consciousness with seizures. In addition, increased ICP would be particularly important as an etiologic factor in producing pulmonary edema. The increased ICP occurred prior to the overload of blood and balanced salt solutions.

Injuries to the central nervous system may be associated with the development of acute pulmonary edema even in the absence of overt left ventricular disease.[5-8] Cameron and De[5] produced edema in dogs by injecting fibrin into the 4th ventricle. Sarnoff and Sarnoff[6] confirmed these observations and showed that sympathectomy ameliorated the pulmonary liquid accumulation; hypothalamic lesions (hemorrhage, infectious, neoplastic, or traumatic) may be the critical factor by causing adrenergic overactivity. This produces shifts in blood from the systemic to the pulmonary circulation, loss of left ventricular compliance, with left atrial and pulmonary capillary hypertension and subsequent edema.[7] Indeed, a variety of sympatholytic, antiepinephrine, or general anesthetic agents appear to relieve experimental neurogenic pulmonary edema.[8]

Grosfeld's group[9] reported a 24% incidence of intraabdominal complications (perforation of the colon and bladder, intraabdominal CSF cyst, and intestinal obstruction due to volvulus) following VP shunt. Certainly these reported intraabdominal complications could not be ruled out preoperatively. On the other hand, our diagnoses were further complicated by an underlying hematologic disorder.

The sex-linked genetic deficiency in hemophilia is related to reduced AHF activity.[2] With most methods, AHF levels in the normal population vary between 50 and 200% but are constant in each individual if blood is drawn under the same circumstances. In patients afflicted with severe hemophilia, the AHF level is almost invariably below 2%, but it may be as high as 20% in mild cases.[1] Most investigators agree

that an AHF level of at least 30% of normal must be achieved during operation, and that levels not lower than 15 to 30% be maintained constantly during the healing process.[10]

Our pediatric patient presented a problem in repletion of factor VIII. The requirement for very large amounts of fresh frozen plasma (FFP) during surgical management tends to induce severe hypervolemia. Originally, FFP was administered to correct the supposed hypovolemia while simultaneously giving AHF. However, cryoprecipitate fractions obtained from FFP and allowed to thaw slowly may yield 50% of the original factor VIII. It is relatively easy to prepare, is obtainable from most blood banks, and obviates the potential hypervolemia from FFP. In our patient, postoperative AHF requirements were met with these concentrates.

Although this case presented a myriad of problems, encouraging results can now be obtained with increasing experience and the availability of fresh frozen plasma and AHF concentrates. With close cooperation among the anesthesiologist, surgeon, and blood bank, life-saving procedures can now be undertaken for acute or elective surgical procedures in hemophiliacs. Nevertheless, one must be prepared to carefully monitor AHF levels and to maintain adequate dietary and metabolic care during the generally protracted postoperative course.

REFERENCES

1. Pechet L, Glaser B: Problems of the hemophiliac during surgical treatment. Anesthesiology 27:399-408, 1966

2. Aldrete JA: Hematologic diseases, Anesthesia and Uncommon Diseases. Edited by J Katz, LB Kadis. Philadelphia, WB Saunders Company, 1973, pp 268-272

3. Tillotson JR, Finland M: Bacterial colonization and clinical superinfection of the respiratory tract complicating antibiotic treatment of pneumonia. J Infect Dis 119:597-624, 1969

4. Downs JB, Chapman RL Jr, Modell JH, et al: An evaluation of steroid therapy in aspiration pneumonitis. Anesthesiology 40:129-135, 1974

5. Cameron GR, De SN: Experimental pulmonary oedema of nervous origin. J Pathol 61:375-387, 1949

6. Sarnoff SJ, Sarnoff LC: Neurohemodynamics of pulmonary edema. II. The role of sympathetic pathways in the elevation of pulmonary and systemic vascular pressures following the intracisternal injection of fibrin. Circulation 6:51-62, 1952

7. Simmons RL, Martin AM Jr, Heisterkamp CA III, et al: Respiratory insufficiency in combat casualties. II. Pulmonary edema following head injury. Ann Surg 170:39-44, 1969

8. Bean JW, Beckman DL: Centrogenic pulmonary pathology in mechanical head injury. J Appl Physiol 27:807-812, 1969

9. Grosfeld JL, Cooney DR, Smith J, et al: Intra-abdominal complications following ventriculoperitoneal shunt procedures. Pediatrics 54:791-796, 1974

10. Brinkhaus JM: The Hemophilias. Chapel Hill, University of North Carolina Press, 1964, p 69

An Unusual Complication of Lumbosacral Plexus Block: A Case Report

STANLEY MURAVCHICK, PhD, MD*
WILLIAM D. OWENS, MD†
St. Louis, Missouri‡

Lumbosacral plexus block is a valuable anesthetic technic in the hands of an experienced anesthesiologist. However, as illustrated by this case report, anesthetic dosage must be selected with great care, and patients unable to describe paresthesias should be excluded from use of this procedure.

THIS report describes an unusual complication of an attempt to provide regional anesthesia by means of lumbosacral plexus block in an aged and debilitated patient.

CASE REPORT

An 89-year-old woman with an extensive history of systemic vascular disease was admitted to the hospital for evaluation of pain, cellulitis, and ulcerations of the right foot. A femoral popliteal arterial bypass procedure had been performed on the right leg 4 years earlier for arterial insufficiency. In addition, the patient had a history of arterial hypertension, coronary artery disease, and diabetes mellitus treated with oral hypoglycemic agents. An episode of acute congestive heart failure was reported, but cardiovascular status was now controlled by continuing therapy with furosemide.

Physical examination revealed a thin woman, appearing of stated age, with apparently diminished hearing acuity. Vital signs at admission were recorded as weight, 50 kg; blood pressure, 200/80 torr; pulse irregular and approximately 80 bpm; respiration, 16/min. Auscultation of the chest revealed a few basilar rales. No cardiac murmur was described. Cellulitis and ulceration of the dorsal and medial surfaces of the right foot were noted. The rest of the examination was noncontributory.

On the 3rd day of hospitalization, after evaluation of ECG, blood-chemistry studies, and arteriography, the patient had a right peroneal artery graft performed under spinal anesthesia. The graft subsequently failed, and an above-the-knee amputation of the leg was scheduled for the 7th hospital day. The patient was evaluated preoperatively as being of ASA physical status IV, and the anesthetic plan included a right lumbosacral plexus block without premedication.

The evening before operation, the patient became very confused; after consideration of physical findings, arterial blood-gas evaluation, and diagnostic blood-chemistry studies, it was felt that the patient had become toxic from gangrenous changes in her ischemic extremity. Plans for operation the following morning were unchanged.

The patient arrived at the operating room disoriented and intermittently somnolent. An IV fluid infusion was started and a

*Resident, Barnes Hospital.
†Assistant Professor.
‡Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri 63110.
Paper received: 7/28/75
Accepted for publication: 9/15/75

blood-pressure cuff and ECG leads were applied. Arterial blood pressure was 180/60 torr, pulse rate 80 bpm, and respirations 14/min. After left lateral decubitus positioning, preparation of the skin, and draping, the necessary anatomic landmarks of L_3-L_4 interspace and posterosuperior iliac spine were easily identified. At the point of intersection of the lines drawn across these landmarks, a 22-gauge spinal needle was introduced slowly to a depth of approximately 8 cm. At this point, the patient winced and then withdrew her right leg. Following demonstration of inability to aspirate fluid, 30 ml of a 1% lidocaine solution with 1:200,000 epinephrine was injected and the needle withdrawn. The sensory level of anesthesia was difficult to establish because of the patient's abnormal mental status.

Within 10 minutes of injection, the patient was unresponsive to verbal and sensory stimulation and then became apneic. She was immediately ventilated with 100% O_2 per face mask and oral airway; blood pressure was 95/55 torr and pulse rate 60 bpm. The operative procedure was now begun. The ECG, showing sinus rhythm with occasional atrial premature contractions, was unchanged, and the pupils were in midposition and not dilated. Thirty minutes after lidocaine injection, blood pressure had decreased to 80/40 torr, returning promptly to 100/50 torr following 25 mg of IV ephedrine sulfate. Pulse rate showed only modest changes during both the initial fall in pressure and the response to ephedrine.

Fifty-five minutes after injection, as the surgical procedure was being completed, the patient began to demonstrate weak but definite spontaneous respiratory efforts, and her pupils were central but widely dilated. The trachea was easily intubated without the use of muscle relaxants and she was transported to the recovery room. Ventilation was controlled until there was demonstration of a clinically adequate tidal volume, with apparent full return of muscle strength and marked improvement in alertness. The patient was then extubated and returned to her room. The remainder of the postoperative course was uneventful, and the patient was discharged on the 23rd hospital day.

DISCUSSION

Rapid, unexpected obtundation and respiratory paralysis were serious complications of this regional anesthetic procedure. The absence of focal or localizing neurologic signs either intraoperatively or in the immediate postoperative period would make the possibility of an acute cerebrovascular accident remote. There had been no history or evidence of recurrent transient cerebral ischemic episodes. It was presumed, therefore, that the complications were directly related to the anesthetic itself.

The lumbosacral plexus block was performed using the technic of Winnie's group.[1] However, we reduced the recommended volume of anesthetic agent, 40 ml, to 30 ml, in view of the patient's debilitated condition. Although we could not elicit a classic paresthesia to document needle position, we did obtain a response from the patient which was thought to be a confirmation of correct position of the needle.

Direct IV injection or rapid absorption of lidocaine from the injection site can produce high plasma levels of the drug. Signs of systemic toxicity may include loss of consciousness without associated seizures or cardiovascular collapse,[2] but the gradual onset and slow resolution of the alteration in consciousness suggest an alternative explanation.

The time interval prior to the onset of diaphragmatic paralysis and the fairly rapid return of function suggest epidural spread of the injected anesthetic. An inadvertent subarachnoid injection would be expected to have produced apnea both earlier in onset and of longer duration than was observed. In addition, one would have expected rapid development of profound hypotension following an extensive spinal anesthetic. Within 10 minutes of administration of deliberate spinal anesthesia several days earlier, the patient's mean arterial blood pressure (MAP) fell to 44% of initial value. Multiple IV infusions of ephedrine sulfate were required over the subsequent 2-hour period to maintain blood pressure at acceptable levels. In contrast, the attempt at lumbosacral plexus block produced a slowly progressive, mild hypotension: the minimum MAP, observed 30 minutes after anesthetic injection, was 70% of starting value.

Epidural spread following plexus block anesthesia has been described previously,[3] but with regard to the brachial plexus. Shantha and Evans[4] have explained spinal and epidural-type blocks after peripheral nerve blocks by subpial, subperineural, and interperineural epithelial spread from the

periphery. In addition, Evans and coworkers[5] have described spread of local anesthetic following a paravertebral sympathetic block procedure, producing epidural anesthesia; they claim that this demonstrates extraneural communications between the paravertebral and epidural spaces.

We believe that the generalized arteriosclerotic disease of this patient contributed to the intensity and level of blockade. Bromage[6] has found that segmental analgesia in patients with occlusive vascular disease may spread 1½ to 3 times further than in normal subjects. Certainly, when an epidural anesthetic is performed, reduced dosage of the agent is indicated in the elderly arteriosclerotic individual.

The anesthetic injection in this patient was probably not directly into the epidural space, as the needle was 5 cm from the midline, but we cannot exclude this possibility; with seepage of even a fraction of the total dose of anesthetic, an exaggerated block effect would be expected.

REFERENCES

1. Winnie AP, Ramamurthy S, Durrani Z, et al: Plexus block for lower extremity surgery. Anesth Rev 1:11-16, 1974

2. Adriani J: Twofold effects of local anesthetics. Int. Anesthesiol Clin 1:651-661, 1963

3. Kumar A, Battit GE, Froese AB, et al: Bilateral cervical and thoracic epidural blockade complicating interscalene brachial plexus block: report of two cases. Anesthesiology 35:650-652, 1971

4. Shantha TR, Evans JA: The relationship of epidural anesthesia to neural membranes and arachnoid villi. Anesthesiology 37:543-557, 1972

5. Evans JA, Dobben GD, Gay GR: Peridural effusion of drugs following sympathetic blockade. JAMA 200:573-578, 1967

6. Bromage PR: Exaggerated spread of epidural analgesia in arteriosclerotic patients. Br Med J 2:1634-1638, 1962

Prolonged Neuromuscular Blockade Associated with Trimethaphan: A Case Report

SUSAN L. WILSON, MD*
ROBERT N. MILLER, MD†
CARMEN WRIGHT, CRNA‡
DIANE HASSE, CRNA§

A case of prolonged neuromuscular blockade associated with the administration of trimethaphan to a neurosurgical patient aged 29 is believed to be the possible result of interaction between trimethaphan, a ganglionic-blocking drug, and muscle relaxant. This possibility should be kept in mind when the administration of trimethaphan is being considered.

THE concept of interaction between ganglionic-blocking agents and neuromuscular transmission is not new, although infrequently encountered. The following case report serves as an example of such interaction.

REPORT OF A CASE

A 29-year-old previously healthy man was admitted to the hospital following the sudden onset of a bifrontal headache with brief lapses into unresponsiveness. Physical examination revealed a lethargic, irritable man weighing 66 kg, with slight nuchal rigidity and no lateralizing signs. The results of a lumbar puncture showed an opening pressure of 500 mm H_2O, with bloody cerebrospinal fluid (CSF). Angiography showed an aneurysm at the apex of the basilar artery and another at the left middle cerebral trifurcation. Chest x-ray, ECG tracing, and SMA-12 were within normal limits.

Eleven days after admission, the patient was brought to the operating room for ligation of his basilar aneurysm through a right temporal craniotomy. He was premedicated with pentobarbital (100 mg) and atropine (0.4 mg) IM, 1 hour before induction of anesthesia. Sleep was induced at 0730 hours with IV sodium thiopental (250 mg) and meperidine (30 mg). After pretreatment with d-tubocurarine (6 mg) IV, the patient was given succinylcholine (100 mg) to facilitate intubation of the trachea, and a 9-mm cuffed endotracheal catheter was placed in the trachea without difficulty. The monitors chosen for this patient included a continuous ECG, a precordial stethoscope, and an esophageal temperature probe. A Doppler monitor was used for auscultation of blood pressure in the upper extremity, insertion of a Foley catheter allowed continuous observation of urine output, and a spinal needle was placed in the subarachnoid space to

*Resident, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri 63110.

†Associate Professor, Department of Anesthesiology, Washington University School of Medicine.

‡Instructor, Department of Nurse Anesthesia, Barnes Hospital, St. Louis, Missouri.

§Student, Department of Nurse Anesthesia, Barnes Hospital.

Reprint requests to Dr. Wilson, Assistant Professor of Anesthesiology, UCLA School of Medicine, Department of Anesthesiology, Wadsworth VA Hospital, Los Angeles, California 90073.

Paper received: 5/21/75
Accepted for publication: 10/26/75

indicate the clarity and flow characteristics of the CSF.

Between 0730 and 1000 hours, the patient was given incremental doses to a total of 54 mg d-tubocurarine (dTc), 50 mg meperidine, and 450 mg sodium thiopental IV. He was ventilated with N_2O-O_2 (67:33%) at a rate of 14 times/min, with a 750 ml tidal volume. Blood pressure had been reduced through the combined use of trimethaphan and halothane to 60/40 torr at 1025 hours. The lowest systolic blood pressure reached was 30 torr. The duration of the hypotensive period was 75 minutes. The trimethaphan and halothane were discontinued at 1135, following entrapment of the aneurysm, and the blood pressure returned to 110/40 torr after 3 phenylephrine IV washes. Total dose of trimethaphan was 4500 mg during the 90-minute period of administration.

The patient had been allowed to cool to an esophageal temperature of 35 C, noted at 1130, but the temperature had risen to 36° by 1230. Urine output during the procedure was greater than 100 ml/hr, 100 ml being eliminated the 1st hour after discontinuing the trimethaphan. A total of 5000 ml of fluid, including 2000 ml D/5 normal saline solution, with trimethaphan 2000 ml D/5 lactated Ringer's solution, and 1000 ml lactated Ringer's solution were administered during the procedure; no blood was administered. At the conclusion of the operation at 1315 hours, the patient was given atropine (1.8 mg) and neostigmine (4 mg) and N-allyl oxymorphone (0.2 mg) IV. During the next 25 minutes, the patient remained apneic and was hypoventilated to allow an increase in $Paco_2$ to stimulate ventilation.

However, he showed no demonstrable reversal of neuromuscular blockade. There was no response to ulnar nerve stimulation by Block-Aid® monitor. Arterial blood withdrawn at 1340 hours revealed a significantly elevated $Paco_2$ and commensurately lowered pH, consistent with deliberate hypoventilation. More vigorous ventilation was instituted and additional atropine (0.6 mg) and neostigmine (1.5 mg) was given IV. By 1430, the patient was beginning to initiate gross movements of all extremities and was responsive to commands.

He was taken to the recovery room at 1500 hours, where ventilation was assisted with a Bennett respirator at an FIO_2 of 1. Arterial blood withdrawn in the recovery room revealed pH 7.45, $Paco_2$ 27, Pao_2 454. Within another 45 minutes, the patient was able to ventilate spontaneously and had a vital capacity of 1500 ml. At this time, he was extubated. The arterial blood was again sampled, after 10 minutes of O_2 administered by mask, and gave a $Paco_2$ of 33 and Pao_2 of 132, with a pH of 7.38. Serum Na^+, K^+, and Cl^- were within normal limits. The remainder of the postoperative course was uneventful.

Approximately 3 weeks later the patient was again brought to the operating room for resection of the aneurysm involving his middle cerebral artery. The anesthetic technics and agents used were essentially the same as for his previous operation, with the following exceptions:

(1) Total dose of dTc given in increments over the first 2 hours was 69 mg.

(2) Halothane was administered initially, beginning 2 hours after induction, for 110 minutes, with blood pressure maintained at 120/80 torr, at which time the trimethaphan drip was begun with immediate response to 60/40 torr. Total dose of trimethaphan was 35 mg over a 10-minute period. Upon discontinuation of the halothane and trimethaphan, the blood pressure rose to 120/80 torr without administration of a vasopressor. The neuromuscular junction was monitored frequently and post-tetanic facilitation was noted throughout the procedure. At the end of the operative procedure, which lasted 5 hours and 50 minutes, the patient was initiating ventilation before the IV administration of atropine (2 mg) and neostigmine (5 mg). The patient was extubated without difficulty and made an uneventful recovery. He was discharged from the hospital 10 days after the second craniotomy.

DISCUSSION

The problem presented in the care of this patient involves the differential diagnosis of persistent postoperative neuromuscular blockade. Hypocarbia as a cause of postoperative apnea was ruled out early when the patient did not respond to hypoventilation carried to excess. Hypercarbia with acidosis is another cause of postoperative apnea; however, there is no reason to suspect that acidosis existed prior to deliberate hypoventilation. The induced acidosis may have, however, added to the already existing problem. One would expect to find marked cerebral vasodilation and increased cerebral blood flow secondary to an acute

increase in $Paco_2$, as seen when the patient was deliberately hypoventilated.

Hypothermia was not a problem. The patient did not receive any of the drugs commonly recognized to potentiate neuromuscular blockade, such as antibiotics, procaine, quinidine, guanethidine, or cholinesterase inhibitors. Central depression secondary to barbiturate, narcotic, or halothane remains a possibility, as does edema of the brainstem. The total dose of thiopental was not excessive. The concentration of halothane was 1.5% and its total duration of administration was 1 hour. Moreover, the patient had not received halothane for 90 minutes prior to the attempted reversal of neuromuscular blockade. N-allyl-oxymorphone was given but the patient did not respond to the small dose (0.2 mg) given. An abnormality of pseudocholinesterase is unlikely on the basis of the patient's response to his second anesthetic.

There was no history of exposure to cholinesterase inhibitors, but this possibility remains. The initial dose of neostigmine was somewhat less than the 0.07 mg/kg recommended by Churchill-Davidson, but one should still expect some degree of reversal with this dose, particularly since the last dose of dTc had been given some 210 minutes before administration of the reversal drug.

Another possibility is a neurologic (brainstem) catastrophe, which can be ruled out on the basis that this patient finally responded and was neurologically intact. Transient brainstem swelling cannot be ruled out. Serum Na^+ and K^+ before and immediately after operation were within normal limits. Serum Mg^{++} and ionized Ca^{++} were not measured.

Reduced blood flow to tissues, especially muscle and kidney, during induced hypotension could be expected to affect the kinetics of muscle relaxant distribution. With a fall in muscle perfusion, one would expect a delay in removal of displaced nondepolarizing relaxant drug from the neuromuscular junction, thereby prolonging the neuromuscular block. In this patient, blood pressure was restored by several IV phenylephrine washes. Renal blood flow appeared adequate at all times because of the acceptable urinary output, but one cannot be sure of the total perfusion to the muscle mass. Thus, the effect of hypotension on redistribution of dTc could help to explain the observed prolonged neuromuscular blockade. However, there was a period of 90 minutes between the restoration of blood pressure and the attempted reversal of the neuromuscular blockade, making a redistribution phenomenon an unlikely explanation.

Finally, a not-so-commonly considered factor, and perhaps the etiologic mechanism in this patient, is the interaction between trimethaphan, a ganglionic-blocking drug, and the muscle relaxant used.

As early as 1949, Randall and associates[1] noted the existence of muscle weakness in dogs treated with trimethaphan. The explanation proposed was associated hypotension rather than a true interaction of the drug with the neuromuscular junction. Later work by Pearcy and Wittenstein[2] showed prolonged apnea in rats with administration of trimethaphan, but without severe depression of blood pressure. In 1957, Tewfik[3] noted prolongation of succinylcholine-induced apnea in patients treated with trimethaphan. He demonstrated *in vitro* that trimethaphan was a potent inhibitor of pseudocholinesterase and postulated that the drug was metabolized by pseudocholinesterase, inducing temporary inhibition.

Pearcy and Wittenstein[2] attempted to test Tewfik's[3] postulate. Their interpretation was that trimethaphan was not destroyed by pseudocholinesterase to any substantial extent. In addition, in rats given large doses of trimethaphan (25 mg/kg), they observed brief periods of apnea resembling the apnea following muscle relaxation.

Deacock and Davies,[4] using a rat-diaphragm model, observed in their preparation that "trimethaphan produced neuromuscular block after 60 mg had been given, but only 20 mg was required after partial curarization," and that "neostigmine increased the degree of neuromuscular block in preparations recovering from trimethaphan."

If trimethaphan (*in vivo* as well as *in vitro*) is a cholinesterase inhibitor, then in large doses as administered to the patient under consideration, one might observe an acetylcholine-induced block. One would expect neostigmine to augment such a neuromuscular inhibition. If trimethaphan is metabolized by serum pseudocholinesterase in man, perhaps one could observe substrate inhibition with very large doses. This problem could be augmented by the administration of neostigmine. Either of the above explanations is possible with respect to the persistent postoperative neuromuscular

blockade observed in this patient. Another possibility is a complex interaction at the neuromuscular junction between ganglion-blocking agents (like trimethaphan) and nondepolarizing muscle relaxants (such as dTc or pancuronium). Such an interaction has been demonstrated in the laboratory by Deacock and Davies.[4]

There appears to be a complex but well established interaction between the ganglionic-blocking agents, trimethaphan, and neuromuscular blockade, at least when very large doses of trimethaphan are used. It would seem advisable to keep this interaction and its possible consequences in mind when considering agents and technics of hypotensive anesthesia, and consider abandoning trimethaphan and switching to another hypotensive technic in patients who, seemingly refractory to the agent, require larger and larger doses to obtain the desired hypotensive effect.

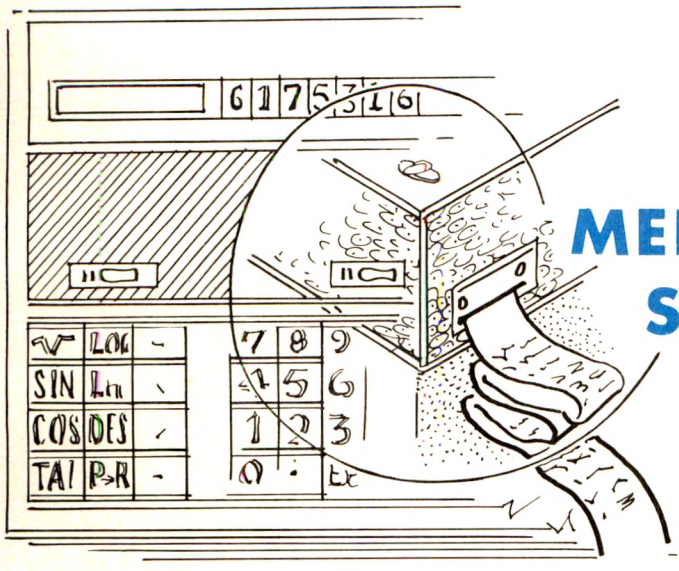
REFERENCES

1. Randall LD, Peterson WG, Lebmann G: The ganglionic blocking action of thiophanium derivatives. J Pharmacol Exp Ther 97:48-57, 1949

2. Pearcy WC, Wittenstein ES: The interactions of trimethaphan (Arfonad), suxamethonium and cholinesterase inhibition in the rat. Br J Anaesth 32:156-159, 1950

3. Tewfik GI: Trimethaphan, its effect on the pseudo-cholinesterase level of man. Anaesthesia 12:326-329, 1957

4. Deacock AR, Davies TDW: The influence of certain ganglionic blocking agents on neuromuscular transmission. Br J Anaesth 30:217-225, 1958



MEDICAL STATISTICS

Statistical Pearls. II How Often Did That Happen?

PATRICK D. HARRIS, PhD*

TOM MUSACCHIA, the young internist and budding researcher, hurried to catch David Wiegman, who was considered to be the best at the numbers game. "David!" "Hi, Tom." Dr. Musacchia proceeded to relate his problem. "I have serum total cholesterol on 110 male patients that I want to use as a control group for a lipid metabolism study. The *mean* is a little high, but I'll never be able to show any significant differences with the range that I have in this control group." David thought for a moment, and then, "Does your distribution look good?"

"Distribution?" Tom asked. "I just assumed a *normal curve*."

"Well, Tom, you have enough observations to get at least a feel for the homogeneity of your control group. You might have a large range because your control data are derived from more than one statistical population."

Since Dr. Musacchia was not familiar with technics of looking at distributions, Dr. Wiegman described a simple, but reasonably accurate approach to the construction of a *histogram*.[1] Cholesterol had been measured to the nearest 1 mg/100 ml to give a mean value of 267 mg/100 ml, with a range of 145 to 437 mg/100 ml. Since 8 to 15 *class intervals* of equal size are desirable for a histogram, an initial value of 140 mg/100 ml and a class interval of 20 mg/100 ml (437 − 145 = 292 mg/100 ml range; 292/15 ≒ 20 mg/100 ml for the interval size) were arbitrarily chosen. This gave class intervals of 140-159, 160-179, 180-199, 200-219, 220-239, 240-259, 260-279, 280-299, 300-319, 320-339, 340-359, 360-379, 380-399, 400-419, and 420-439. The starting point of 140 mg/100 ml was selected so that the mean value for the data (267 mg/100 ml) fell close to the midpoint (269.5) of one of the class intervals (260-279).

*Investigator, Dalton Research Center; Associate Professor of Physiology, University of Missouri School of Medicine, Columbia, Missouri 65201.

Following this choice of intervals, a *frequency table* was obtained by counting the number of cholesterol measurements that fell within each interval. Dr. Wiegman illustrated this procedure by noting that, of the total of 110 measurements, there was only one value (145 mg/100 ml) which fell in the 140-159 interval. Thus, the frequency was 1 for the 140-159 class interval. The measurements 160 and 171 mg/100 ml were the only values in the 160-179 class interval, so the frequency was 2 for that interval.

Dr. Wiegman explained that a histogram is merely a vertical bar graph in which the width of each bar is the class interval and the height of each bar is the frequency for that interval. He also emphasized that it is easier to compare 2 histograms if the frequency for each class interval in a histogram is expressed as a percentage of the total number of measurements in that histogram.

Dr. Musacchia obtained the frequency table, drew the bar graph, returned to Dr. Wiegman's office, and presented his chart (fig 1), remarking: "Well, I guess I have a normal distribution." After a minute of study, Dr. Wiegman commented: "This distribution is fairly symmetrical, but I wonder about the shape. Most of the time, a homogeneous group of data will have a mean that falls in, or next to, the class interval that has the highest frequency. In this distribution, the highest frequency occurs for the class interval 220-239 while the mean (267) is located 2 class intervals away (in 260-279). In addition, I would expect the frequency to decrease for the class intervals on either side of the mean. But, Tom, your data have 5 class intervals which have about the same frequency. This suggests a nonhomogeneous group of data. I would recommend that you go back to the raw measurements and try to divide them into at least 2 groups on the basis of some characteristic in the histories of these patients."

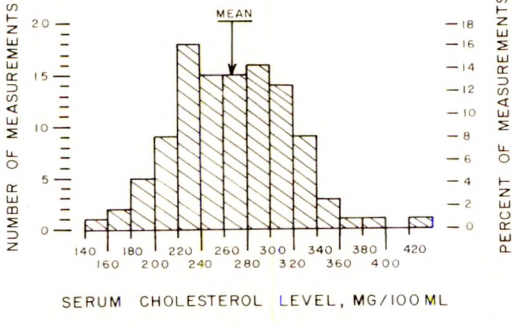


FIG 1. Histogram for 110 measurements of serum total cholesterol. The numbers on the abscissa identify the lowest cholesterol value in each class interval. The left ordinate scale gives the height of each bar as the *number* of measurements which fell within each class interval. The right ordinate scale gives the height of each bar as the *percentage* of total measurements which fell in each class interval.

Dr. Musacchia knew that a number of the patients in his control group had a history of myocardial infarction, but these patients were stable, with no significant weight changes and no special diets. Yet, it has been proposed that atherosclerosis in man is related to a disorder of lipid metabolism.[2,3] So he classified his patients into those who had the *attribute of a prior myocardial infarction*[3] and those with the *attribute of no history of myocardial infarction*.[2] He then obtained a frequency table and constructed a histogram for each of these 2 groups.

"David, this is amazing! I want you to look at these distributions (fig 2) for pa-

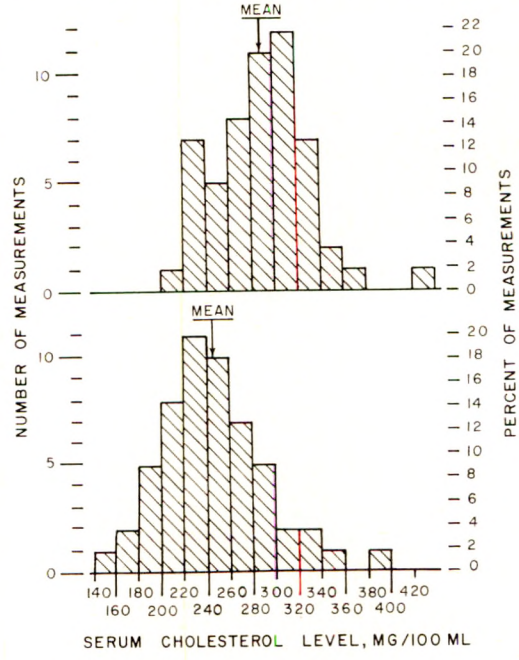


FIG 2. Bottom panel: Histogram for measurements of serum total cholesterol from 55 patients who had no prior history of myocardial infarction. These data were derived from the statistical characteristics of the Harvard group in reference 2 and are contained in the histogram in figure 1. Top panel: Histogram for measurements of serum total cholesterol from 55 patients (ages 40-59) who had a previous history of myocardial infarction. These data were derived by adding 20 mg/100 ml to each of the values in the Appendix Table A in reference 3. These data are also contained in the histogram in figure 1.

tients with and without a prior history of myocardial infarction!" Dr. Wiegman studied the graphs for only a brief moment. "I do believe you have something, Tom. In the noninfarcted group (fig 2, bottom panel), the mean is 245 and is very close to the interval (220-239) with the peak frequency. In the infarcted group (fig 2, top panel), the mean is 290 and is also close to the interval (300-319) with the peak frequency. In both histograms, there is a reasonably good decrease in frequency for class intervals on each side of the peak frequency. The class interval 220-239 for the group of infarcted patients is somewhat unusual, but you would need more measurements before you could further subdivide this group of infarcted patients. In general, one needs at least 8 class intervals and 40 observations to make a reasonable attempt to *describe data by a histogram*."

"Thanks, David. It is now apparent that I should limit the control and experimental groups in my lipid metabolism study to patients without a history of myocardial infarction. On the other hand, I could also have control and experimental groups of patients who have previously infarcted. Their lipid metabolism might be considerably different in comparison to noninfarcted patients."

"Just think, Tom, this point was almost missed because you calculated a *mean* and range as the *first* step in looking at your data." Tom thought for a moment. "David, I sure didn't *mean* to do that."

REFERENCES

1. Simpson GG, Roe A, Lewontin RC: Quantitative Zoology. New York, Harcourt, Brace and World, Inc, 1960, pp 31-47

2. Lewis LA, Olmsted F, Page IH, et al: Serum lipid levels in normal persons. Findings of a cooperative study of lipoproteins and atherosclerosis. Circulation 16:227-245, 1957

3. Lawry EY, Mann CV, Peterson A, et al: Cholesterol and beta lipoproteins in the serums of Americans. Am J Med 22:605-623, 1957

The Effect of Enflurane, Isoflurane, Fluroxene, Methoxyflurane and Diethyl Ether Anesthesia on Ouabain Tolerance in the Dog

ANTHONY D. IVANKOVICH, MD*
DAVID J. MILETICH, PhD†
RONALD K. GROSSMAN, MD‡
RONALD F. ALBRECHT, MD§
ADEL A. EL-ETR, MD‖
VINCENT J. CAIROLI, PhD**

Digitalis tolerance in dogs anesthetized with enflurane, isoflurane, fluroxene, methoxyflurane, and diethyl ether was compared with that in dogs anesthetized with pentobarbital. Ouabain dosage needed to cause ventricular tachycardia was significantly higher than that of pentobarbital with all agents except fluroxene, as was the LD_{50}. The relative potency of these anesthetics in converting ouabain-induced ventricular tachycardia to sinus rhythm, in order of descending effectiveness, was: diethyl ether, methoxyflurane, enflurane, fluroxene, isoflurane, pentobarbital.

THE effect of anesthetic agents on digitalis tolerance is of considerable practical as well as theoretic interest, especially with a burgeoning geriatric population calculated to increase the incidence of digitalized surgical patients. Since the therapeutic index for digitalis glycosides is quite small, knowledge concerning digitalis-anesthetic interactions is imperative in selecting safe, effective drug combinations.[1,2]

Previous investigators have demonstrated digitalis toxicity to be reduced by epidural[3] or systemic lidocaine,[4] halothane,[5] and methoxyflurane,[6] increased by cyclopropane,[5] and unchanged by barbiturates.[5,7] In 1971 and subsequently, we reported that ketamine and neuroleptanesthesia increased tolerance to digitalis-induced arrhythmias.[8,9] This report extends information on the digitalis-anesthetic interaction for some standard and experimental anesthetic agents.

METHODS

Two series of experiments were performed on 120 unpremedicated dogs, each weighing between 15 to 20 kg. In the first series, 60 dogs were divided into 6 equal groups, according to the anesthetic employed: (1)

*Chairman, Department of Anesthesiology, Illinois Masonic Medical Center, Professor of Anesthesiology, University of Illinois, Abraham Lincoln School of Medicine, Chicago, Illinois.

†Director of Anesthesia Research, Michael Reese Medical Center, Chicago, Illinois.

‡Clinical Assistant Professor of Anesthesiology, University of Illinois, Abraham Lincoln School of Medicine, Chicago, Illinois.

§Chairman, Department of Anesthesiology, Michael Reese Medical Center, Professor of Anesthesiology, University of Chicago, Pritzker School of Medicine, Chicago, Illinois.

‖Professor and Chairman, Department of Anesthesiology, Loyola University, Stritch School of Medicine, Maywood, Illinois.

**Director of Anesthesia Research, Illinois Masonic Medical Center, Chicago, Illinois.

Paper received: 7/7/75
Accepted for publication: 8/26/75

pentobarbital (control), (2) fluroxene, (3) isoflurane, (4) methoxyflurane, (5) enflurane, and (6) diethyl ether, and digitalis tolerance was determined by ascertaining the ouabain dosage required to produce ventricular tachycardia (VT) and death.

After achieving satisfactory anesthesia using a face mask for the inhalational anesthetics, or an induction dose of 35 mg/kg IV for pentobarbital, the animals were intubated endotracheally with a cuffed tube and respiration was controlled by a Harvard respiratory pump using 100% O_2. The femoral artery was cannulated to monitor arterial blood pressure, and a femoral vein was cannulated for ouabain infusions. In pentobarbital-anesthetized dogs, both femoral veins were cannulated, one for continuous administration of ouabain and the other for intermittent administration of pentobarbital. An ECG (lead II) and arterial blood pressure were continuously displayed, and tracings were recorded as appropriate. Heart rate was determined from the ECG record. Arterial blood gases were measured periodically, and arterial concentrations of the anesthetic agents were analyzed by flame ionization detector.[10] Ventilation was adjusted to maintain $Paco_2$ at approximately 35 torr, and any base deficit in excess of 5 mEq/L was corrected with $NaHCO_3$. Temperature was maintained between 37 and 39 C.

Ouabain was administered by constant-infusion pump at a rate of 35 mcg/kg/hr. The cumulative dose of ouabain required to produce VT (3 or more consecutive premature ventricular contractions) and death was determined for each animal and then averaged for each group. Results were analyzed for statistical significance by fixed analysis of variance within each group.

In the second series, 60 animals were anesthetized with pentobarbital, intubated, ventilated with 100% O_2, and managed exactly as were the dogs in the pentobarbital group in the first part of the study. Ventricular tachycardia was induced by continuous infusion of ouabain (35 mcg/kg/hr). About 3 minutes after the onset of VT, either 150 mg of pentobarbital was given IV or 5 to 7% of enflurane or isoflurane, 8 to 10% fluroxene, 2 to 3% methoxyflurane, or 15 to 25% of diethyl ether was introduced into the anesthetic system. The ouabain infusion was continued during these maneuvers. Immediately following conversion of VT to sinus rhythm, arterial blood was withdrawn for the estimation of blood gases and anesthetic blood levels.

RESULTS

1. *Ventricular Tachycardia* (fig 1).—The mean dose of ouabain (in mcg/kg) required to produce VT in dogs anesthetized with pentobarbital was 53.4; with fluroxene, 60.1; with isoflurane, 69.4; with methoxyflurane, 81.3; with diethyl ether, 90.4; and with enflurane, 92.8. The ouabain dosage for the last 4 anesthetics was significantly higher than that for pentobarbital ($p<0.01$ to 0.005). The difference in dosage between fluroxene and pentobarbital was not statistically significant.

2. *Mean Lethal Dose* (MLD) (fig 2).—The MLD of ouabain (in mcg/kg) in dogs

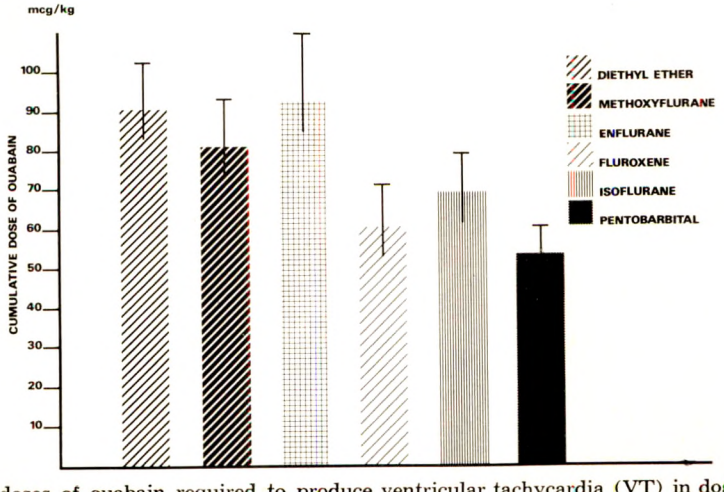


FIG 1. Average doses of ouabain required to produce ventricular tachycardia (VT) in dogs anesthetized with agents studied. Each value represents mean and SD of 10 experiments.

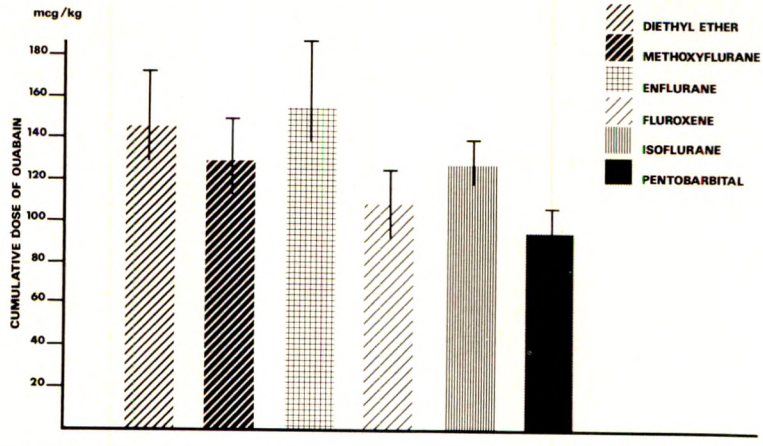


FIG 2. Average lethal doses of ouabain in dogs anesthetized with agents studied. Each value represents mean and SD of 10 experiments.

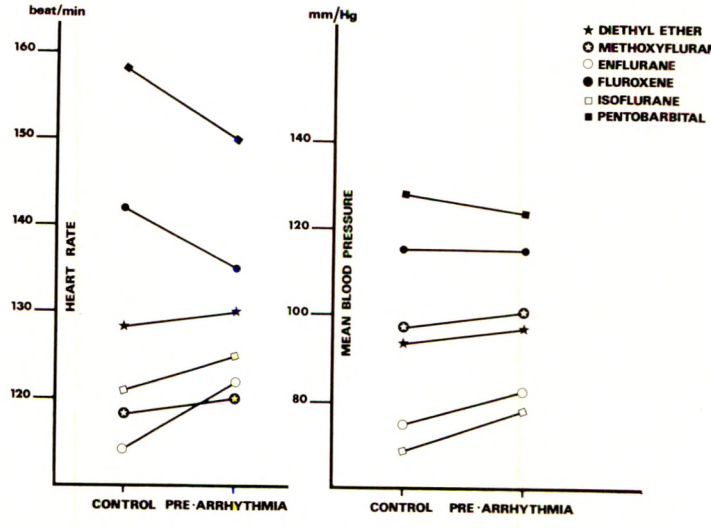


FIG 3. Average heart rates and MAP during ouabain infusion. Control values were calculated just before ouabain administration and prearrhythmia values were determined immediately before appearance of VT. Each value represents mean of 10 experiments.

anesthetized with pentobarbital was 95.2; with fluroxene, 108; with isoflurane, 127.5; with methoxyflurane, 128.9; with diethyl ether, 145.1; and with enflurane, 156.4. The dosage for isoflurane, methoxyflurane, diethyl ether, and enflurane was significantly higher than for pentobarbital.

The difference in dosage between fluroxene and pentobarbital again was not statistically significant. Death in pentobarbital-anesthetized animals was almost always due to ventricular fibrillation, while dogs anesthetized with the other agents invariably died in cardiac asystole.

3. *Mean Heart Rate and Blood Pressure Values* (fig 3).—Control values for heart rate and blood pressure were taken before the ouabain infusion was started, and prearrhythmia values were determined just before the appearance of premature ventricular contractions. Both control and prearrhythmia mean blood pressures and heart rates were lower for isoflurane, methoxyflurane, enflurane, and diethyl ether than for pentobarbital or fluroxene. These parameters did not change significantly during digitalization in any of the groups.

4. *Effects of Anesthetic Agents on Ouabain-Induced VT* (fig 4).—Since previous studies[3,9] indicated that 5 minutes or less after the onset of VT was an optimal time to administer agents for conversion of VT

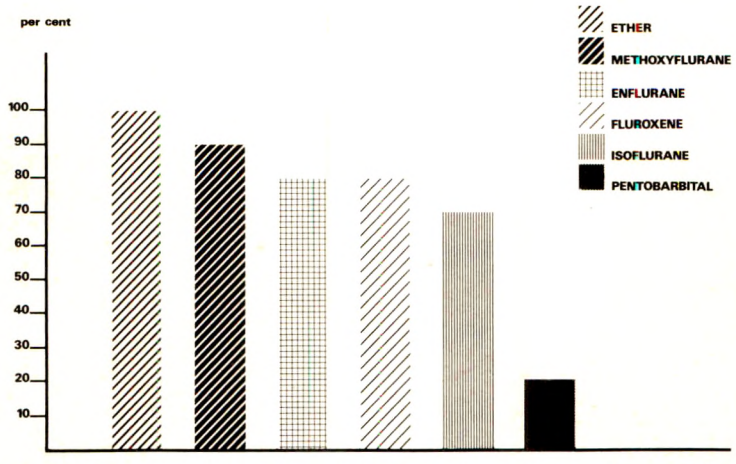


FIG 4. Percentage of dogs converted to sinus rhythm by each anesthetic, subsequent to an initial 3-minute oaubain-induced VT. Each value is based on 10 dogs per anesthetic agent.

to sinus rhythm, the 6 agents under study were administered 3 minutes after the onset of VT, and the ouabain infusion was continued. The intervention of the anesthetics resulted in the following conversions of VT to sinus rhythm: diethyl ether, 10/10 dogs; methoxyflurane, 9/10; enflurane and fluroxene, 8/10; isoflurane, 7/10; and pentobarbital, 2/10. The average time from the administration of the anesthetic until conversion was approximately 1 minute for diethyl ether, and between 3 and 4 minutes for the other general anesthetics. The mean arterial blood concentration following conversion of VT to sinus rhythm (in mg %) was 25.5 for diethyl ether; 8.3 for methoxyflurane; 7.9 for enflurane; 12.3 for fluroxene; and 6.9 for isoflurane. These experiments were terminated shortly after conversion of VT to sinus rhythm was established.

Mean blood pressures before and after conversion of VT to sinus rhythm are shown in figure 5. On a percentage basis, the smallest decrease in blood pressure (9%) was seen following conversion with pentobarbital and with diethyl ether. Pentobarbital was least effective and diethyl ether most

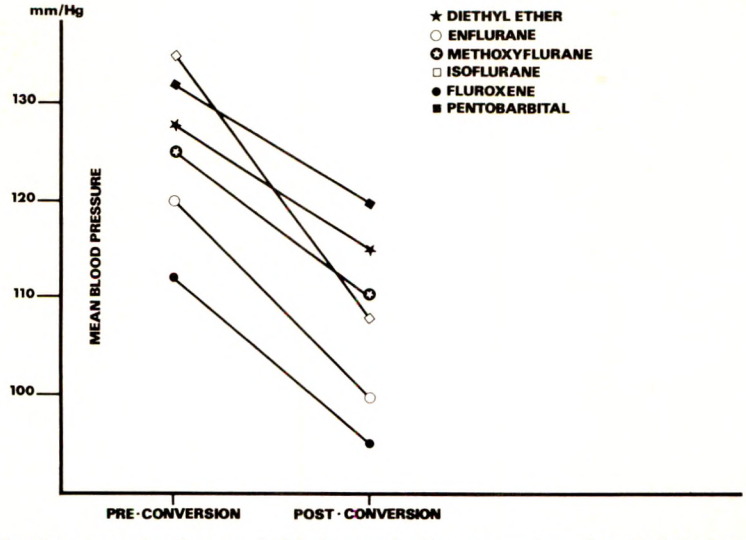


FIG 5. Mean blood pressure levels recorded before and after conversion of oaubain-induced VT to sinus rhythm. Preconversion values were recorded during pentobarbital anesthesia and represent the average during 3 minutes of ouabain-induced VT. Postconversion values were recorded immediately after conversion to sinus rhythm. Each value represents the mean for only those dogs successfully converted.

effective in converting VT to sinus rhythm, suggesting that decreased blood pressure was not the sole factor in VT conversion.

DISCUSSION

At full digitalization, a patient will have received more than 60% of the toxic dose, while at the onset of toxicity, he will have received as much as 50% of the lethal dose. Given this narrow margin of safety between the full therapeutic, toxic, and lethal doses, any modification of digitalis action, particularly by drug interactions, can easily result in under- or overdigitalization. As previously reported,[11] a number of diverse factors possess this capability: drugs, electrolyte disturbances, autonomic nerve function, hypoxia, changes in blood pH, and body temperature, among others.

Morrow was one of the first to demonstrate that anesthetic agents significantly modify the effects of digitalis glycosides (ouabain, digoxin). He reported that tolerance to digitalis toxicity was increased by halothane, decreased by cyclopropane, and unchanged by pentobarbital, with no effect on the therapeutic positive-inotropic response.[5-7] The clinical importance of this subtle phenomenon for the anesthesiologist pertains to both digitalized and undigitalized patients. If an anesthetic increases tolerance to digitalis, a fully digitalized patient becoming underdigitalized during anesthesia may develop heart failure, while in a fully digitalized patient anesthetized with agents which decrease tolerance to digitalis, arrhythmias and other signs of digitalis toxicity might appear during the anesthetic period. Also, if a previously undigitalized patient develops heart failure during anesthesia, more digitalis might be needed to achieve a therapeutic effect, were the patient anesthetized with an agent that increases tolerance to digitalis. Following emergence from anesthesia, when the protective effect of the anesthetic is lost, this patient might develop digitalis intoxication.

The present study shows that diethyl ether, methoxyflurane, enflurane, and isoflurane increased tolerance to digitalis toxicity when administered before ouabain infusion and restored sinus rhythm when administered acutely during ouabain-induced VT. However, while pretreatment with fluroxene did not affect myocardial sensitivity to ouabain toxicity, when fluroxene was administered acutely during ouabain-induced VT, it successfully converted 8/10 dogs to sinus rhythm. These results emphasize that in cases of digitalis toxicity, a drug useful for therapy may not necessarily be the drug of choice for prophylaxis.

Halothane and methoxyflurane have been reported to produce a dose-dependent increase in the atrioventricular functional refractory period, independent of autonomic nervous-system activity.[6] In addition, there is evidence that halothane decreases intrinsic ventricular automaticity:halothane depressed ventricular escape pacemaker activity during vagal stimulation before and after ouabain-induced VT,[12] and suppressed spontaneous phase-4 depolarization in Purkinje fibers *in vitro*.[13] Thus, halothane and methoxyflurane possess characteristic intrinsic, antiarrhythmic properties which could explain the increased tolerance to ouabain toxicity, as well as the reversal of ouabain-induced VT, observed in this study.

The sympathetic nervous system is stimulated by digitalis at all levels, from central to peripheral sites, and is believed to be involved in the genesis of digitalis-induced ventricular arrhythmias.[14] Thus, anesthetics such as cyclopropane, which enhance sympathetic activity, also increase digitalis toxicity. Conversely, there is evidence that halothane[15] and isoflurane[16] decrease sympathetic nervous activity which may contribute to the increased tolerance to digitalis toxicity conferred by these agents.

It has been reported[17] that an increase in blood pressure decreases the threshold for the genesis of arrhythmias, perhaps due to the related augmentation of sympathetic nervous activity, or an increased cardiac afterload. Consequently, the decrease in blood pressure produced by the more effective inhalational anesthetics in this study may be an ancillary factor in further protecting against digitalis toxicity.

Heart rate is known to influence both the therapeutic and toxic actions of digitalis, presumably mediated via ion-exchange mechanisms involving calcium and potassium.[18] An increase in heart rate has been shown to increase K^+ efflux, with a concomitant decrease in myocardial K^+, considered a major mechanism of digitalis toxicity.[19] Thus, there is an inverse relationship between heart rate and the toxic or lethal dose of ouabain.[20] However, as this phenomenon appears to be more important at higher heart rates,[18] the decrease in such rates produced by anesthetic agents is probably a minor factor in their protective action against digitalis toxicity.

Another possibility for an antiarrhythmic property has been revealed by recent studies with ^{42}K exploration of the effects of anesthetics on K^+ movements.* Preliminary data indicate that halothane and methoxyflurane decrease K^+ efflux, preventing the intracellular loss of this ion. Thus, these inhalational anesthetics may stabilize excitable membranes and exert an antiarrhythmic action similar to that of local anesthetics.

*Ivankovich, AD: Unpublished data, 1972.

REFERENCES

1. Rodenski PL, Wasserman F: Observations on digitalis intoxications. Arch Intern Med 108:171-188, 1961

2. Beller GA, Smith TW, Abelman WH, et al: Digitalis intoxication. A prospective clinical study with serum level concentrations. N Engl J Med 284:989-997, 1971

3. Wilson D, Paradise RR, Stoelting VK: Alteration of toxic manifestations of acetyl strophanthidin by epidural block. Anesth & Analg 43:729-739, 1964

4. Morrow DH, Bosomworth PP: Anesthesia and digitalis toxicity. III. Effect of lidocaine on ouabain-induced ventricular tachycardia. Anesth & Analg 46:183-186, 1967

5. Morrow DH, Townley NT: Anesthesia and digitalis toxicity: an experimental study. Anesth & Analg 43:510-519, 1964

6. Morrow DH, Haley JV, Logic JR: Anesthesia and digitalis. VII. The effect of pentobarbital, halothane, and methoxyflurane on the A-V conduction and inotropic responses to ouabain. Anesth & Analg 51:430-438, 1972

7. Morrow DH: Anesthesia and digitalis toxicity. VI. Effects of barbiturates and halothane on digoxin toxicity. Anesth & Analg 49:305-309, 1970

8. Ivankovich AD: Effect of ketamine on neuroleptanesthesia on digitalis tolerance. Atlanta, Georgia, Proceedings of the American Society of Anesthesiologists Annual Meeting, 1971, pp 163-164

9. Ivankovich AD, El-Etr AA, Janeczko GF, et al: The effects of ketamine and of Innovar® anesthesia on digitalis tolerance in dogs. Anesth & Analg 54:106-111, 1975

10. Lowe HJ: Flame ionization detection of volatile organic anesthetics in blood, gases, and tissues. Anesthesiology 25:808-814, 1964

11. Ivankovich AD: Anesthetic management problems posed by therapeutic advances: II. Digitalis and glucagon. Anesth & Analg 51:607-616, 1972

12. Logic JR, Morrow DH: The effect of halothane on ventricular automaticity. Anesthesiology 36:107-111, 1972

13. Reynolds AK, Chiz JF, Pasquet AF: Halothane and methoxyflurane—a comparison of their effects on cardiac pacemaker fibers. Anesthesiology 33:602-610, 1970

14. Pearle DL, Gillis RA: Effect of digitalis on response of the ventricular pacemaker to sympathetic neural stimulation and to isoproterenol. Am J Cardiol 34:704-710, 1974

15. Skovsted P, Price ML, Price HL: The effects of carbon dioxide on preganglionic sympathetic activity during halothane, methoxyflurane, and cyclopropane anesthesia. Anesthesiology 37:70-75, 1972

16. Sapthavichaikul S, Skovsted P: Effects of isoflurane (Forane®) on autonomic nervous activity, arterial pressure and pulse rate. Washington, DC, Proceedings of the American Society of Anesthesiologists Annual Meeting, 1974, pp 239-240

17. Katz RL, Epstein RA: The interaction of anesthetic agents and adrenergic drugs to produce cardiac arrhythmias. Anesthesiology 29:763-784, 1968

18. Vincenzi FF: Influence of myocardial activity on the rate of onset of ouabain action. J Pharmacol Exp Ther 155:279-287, 1967

19. Lee KS, Klaus W: The subcellular basis for the mechanism of inotropic action of cardiac glycosides. Pharmacol Rev 23:193-261, 1971

20. Lahiri PK, Laddu AR: Relationship between heart rate and ouabain toxicity in the dog heart-lung preparation. Jpn Heart J 14:357-365, 1973

Editors share the belief that medical writing is capable of vast improvement. This article is one of a series of personal communications from Charles G. Roland, M.D., former Senior Editor of JAMA, to John T. Martin, M.D., Associate Editor of Anesthesia & Analgesia . . . Current Researches. Dr. Roland is Chairman, Department of Biomedical Communications, Mayo Clinic, Rochester, Minnesota 55901.

Thoughts About Medical Writing

XXXV. "Let's Call It Hebetization"

Dear Tom:

All inventions seem to have at least one thing in common. Each needs a name. Without a name, it can't be talked about.

When Morton finally convinced the medical Brahmins of Boston that "Letheon" worked—by convincing a distinguished group of surgeons at the Massachusetts General Hospital—they were all promptly put in need of a proper descriptive name. Morton's own "Letheon" raised problems at once—it was a trade name and he sought a patent, a most unmannerly thing to do. Besides, several of the surgeons knew perfectly well that the active agent, or one of the active agents, was ether. Its odor is distinctive and was well known even then.

Many names were suggested during the first few months after October 16, 1846. One of these was hebetization.[1] I don't know who contributed this name. But think on it. You might have become a hebetiziologist and an editor for the journal *Hebetization and Analgesia . . . Current Researches.* Even so, I don't suppose it would have changed your life. The name is *not* the thing.

Nevertheless, we don't talk about hebetizing a patient. How did "anesthesia" and its various congeners come to be accepted? Holmes, you say?

Probably every anesthesiologist and anesthetist knows the name of Oliver Wendell Holmes. It was, after all, that great Bostonian who has received credit for recommending the use of the word "anaesthesia" to describe the state of insensibility following the inhalation of ether. But is the credit deserved?

Authorities differ. That epitome of historical linguistic authority, the *Oxford English Dictionary,* does not mention Holmes. "Anaesthesia" (following the British spelling) has been traced to 1721, when Bailey used the word to describe a defect of sensation, as in "Paralytic and blasted Persons."[2] The OED then gives an 1848 authority for a totally modern use of the word—and cites Sir J. Y. Simpson, writing in the *Pharmacological Journal*: "The state of anaesthesia lasted for two or three minutes." "Anaesthetic," in all but one of its several meanings, is also credited to the dour Scot, as is "anaesthetize."

Where is Oliver Wendell Holmes in all this? How did Simpson steal all the glory? Is there a chauvinistic plot by the compilers

of the OED to keep the credit, if not in England, at least in the British Isles?

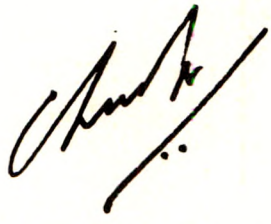
Not really. The OED is based on published—and therefore traceable and verifiable—sources. Holmes' contribution seems to have been made in the form of a letter to W. T. G. Morton, written on November 21, 1846,[3] but apparently not published till 1859.[4] Holmes wrote:

> My Dear Sir,—Everybody wants to have a hand in a great discovery. All I will do is to give you a hint or two, as to names, or the name, to be applied to the state produced and the agent.
>
> The state should, I think, be called "Anaesthesia." This signifies insensibility, more particularly (as used by Linnaeus and Cullen) to objects of touch. (See Good—*Nosology*, p. 259). The adjective will be "Anaesthetic." Thus we might say, the state of anaesthesia, or the anaesthetic state. The means employed would be properly called the anti-aesthetic agent. Perhaps it might be allowable to say anaesthetic agent, but this admits of question.
>
> The words, antineuric, aneuric, neuro-leptic, neurolepsia, neuro-etasis, etc., seem too anatomical; whereas the change is a physiological one. I throw them out for consideration.
>
> I would have a name pretty soon, and consult some accomplished scholar, such as President Everett or Dr. Bigelow, senior, before fixing upon the terms, which will be repeated by the tongues of every civilized race of mankind. You could mention these words which I suggest for their consideration; but there may be others more appropriate and agreeable.
>
> Yours, respectfully,
>
> O. W. Holmes

As his letter shows plainly, Holmes knew that he was suggesting, in "anaesthesia," a word already known to medicine. He proposed an enlargement in the definition of the word, which still is used both to indicate insensibility of touch and to identify the process of general anesthesia. A modern analogy to this method of naming might be the application of "memory" to the guiding principle of genetic replication. A well-known and commonly used word has been broadened in a clearly defined way. This flexibility is a strength of English—so long as definitions are well stated and equally well understood.

And Holmes' role? It would seem to have been less inventive than common mythology would have it, but seminal all the same. And so, even though all this talk of words might conceivably have anesthetized you, it didn't hebetize you.

Regards,



[Charles G. Roland, M.D.]

REFERENCES

1. Sykes WS: Essays on the First Hundred Years of Anaesthesia. Vol 1. Edinburgh, E & S Livingstone, 1960, p 75

2. The Oxford English Dictionary. Edited by JAH Murry, H Bradley, WA Craigie, CT Onions. Vol 1, London, Oxford University Press, 1961, p 301

3. Duncum BM: The Development of Inhalation Anaesthesia: With Special Reference to the Years 1846-1900. London, Oxford University Press, 1947, p 562

4. Holmes OW: Quoted by Rice NP: Trials of a Public Benefactor. New York, Pudney & Russell, 1859

An Evaluation of Memory Under Regional Anesthesia with IV Lorazepam as a Premedicant

HARVEY A. TAUB, PhD*
LOUIS EISENBERG, MD†
Syracuse, New York

Forty male volunteer patients undergoing regional anesthesia were evaluated for alertness and memory in a double-blind study which compared IV lorazepam‡ (4 mg) plus IM meperidine (50 mg) with IV placebo plus IM meperidine (50 mg) as premedicants. The data indicate no significant retrograde effects. Significant differences at all measurement points from 20 minutes to 3 hours following IV drug administration indicated greater sedation and less recall and recognition of events and stimuli (auditory and visual) with the combination of lorazepam and meperidine than with placebo and meperidine. A significant number of patients over age 40 were judged to be excessively sedated after administration of lorazepam. However, respiration, blood pressure, and pulse did not appear to be differentially affected by lorazepam and there were no adverse changes even in patients considered to be oversedated.

NUMEROUS reports have called attention to the desirability of having a premedicant that not only provides sedation but also reduces or eliminates recall of the surgical experience.[1-4] The effects upon memory of the benzodiazepine tranquilizer, diazepam, are well documented, with maximum effects lasting for up to 20 to 30 minutes after IV administration.[2,5,6]

Recent studies suggest that a new benzodiazepine derivative, lorazepam, may be a more potent sedative and have longer-lasting effects upon memory than diazepam.[7-9] The present experiment was designed to provide an extensive evaluation of memory following IV lorazepam premedication for regional anesthesia. Lorazepam and meperidine were compared with placebo plus meperidine in a double-blind evaluation. Stimuli were presented before, during, and after the operative procedure, and memory for these materials was evaluated on the following day.

METHOD

Patient Selection and Anesthetic Procedures.—Forty male volunteers, scheduled to have regional anesthesia for elective surgery, and who met the criteria of having no psychiatric disorders, sensitivity to benzodiazepines or to the glycol base of the drug, or severe visual or auditory impairments, gave written informed consent for participation in the study.

All patients received 50 mg of meperidine and 0.4 mg of atropine IM in their hospital room approximately 1 hour before their operation and were then brought to a holding area (recovery room) where they received the test drug IV. Approximately 20 minutes after IV administration, they were

‡Ativan®: Wyeth Laboratories, Division of American Home Products Corporation.

*Psychology Service, Veterans Administration Hospital; Department of Psychiatry, State University of New York, Upstate Medical Center, Syracuse, New York 13210.

†Section of Anesthesiology, Veterans Administration Hospital; Department of Anesthesiology, State University of New York, Upstate Medical Center.

This study was performed as part of Veterans Administration Research Project No. 2255-01. It was supported in part by a grant from Wyeth Laboratories, Philadelphia, Pennsylvania.

Paper received: 10/14/75

Accepted for publication: 11/17/75

taken into the operating room. For half the patients, the IV test drug consisted of 4 mg of lorazepam in a glycol base, while the rest received a placebo (glycol base only). The use of identical syringes and prearranged random orders permitted a double-blind procedure so that neither the physicians nor the patient knew whether lorazepam or placebo had been administered. Each identical 2 ml syringe was prepackaged to be half full of lorazepam or placebo and was diluted with an equal volume of saline solution prior to use.

Analysis of patient characteristics and surgical procedures after the code was broken indicated that the random and blind assignments produced groups that were equated. There were no differences in age or weight (table 1), type of operative procedures (table 2), or length of operations (89.6 min for lorazepam versus 91.7 min for placebo). Physical status was similar, and in both groups approximately 50% of the patients were in each of the ASA ratings of I and II. Seventeen patients (85%) in each group underwent surgery with spinal anesthesia, the rest receiving either an epidural (n=2) or an IV block (n=1).

One patient in the placebo group was excluded from further participation in the study, since a proper level of spinal anesthesia could not be attained and general anesthesia had to be administered. Thus, the placebo group was reduced to 19 for the remainder of the study. Two additional placebo patients received supplementary meperidine (40 mg), N_2O (70%), and either halothane (n=1) or methoxyflurane (n=1) near the middle or end of the surgical procedure. The data for these patients have been included, since these additional anesthetics were administered after the surgical portion of the memory stimuli were presented and since they did not appear to affect the scores.

TABLE 1
Age and Weight of Volunteer Patients

	Lorazepam		Placebo	
	Mean	Range	Mean	Range
Age	40.6	23-63	40.0	23-65
Weight kg	78.8	60.8-90.7	74.4	47.6-96.6

TABLE 2
Surgical Procedures Performed

	Lorazepam	Placebo
Inguinal hernia	4	3
Pilonidal cystectomy	2	4
Orthopedic	6	5
Rectal	4	1
Urologic	1	4
Superficial extremity procedures	3	3

MEMORY TESTING PROCEDURES

Stimuli.—Both visual and auditory stimuli were used. The visual stimulus was a 10 x 25-cm picture of a dollar bill. The auditory stimuli consisted of 3 different word-pairs (eg, furniture—chair) and 3 different sounds (eg, a fire engine) which were taped in an alternating pattern starting with a word-pair (stimulus 1) and ending with a sound (stimulus 6). To reduce the possibility of bias from specific stimuli, 2 completely different tapes were constructed.

Both stimulus tapes contained a 1-minute volume adjustment section ("testing, 1, 2, 3") which preceded the 6 alternating word-pairs and sounds. Each stimulus presentation period was also approximately 1 minute long. For any particular word-pair presentation, the stimulus was first identified and then was repeated 3 times. For each sound presentation, the stimulus was identified 4 times by name and then played for 20 seconds. After each stimulus, the patient was requested to repeat aloud the words or to name the sound, to demonstrate that he heard the material.

Each stimulus was used to evaluate memory during a different portion of the surgical experience. Stimulus 1 evaluated possible retrograde effects and was presented approximately 3 minutes before administration of the IV test drug. Stimuli 2-5 were presented in the operating room and were designed to evaluate memory during the first 90 minutes after administration of the test drug. They were presented at successive 20 to 25-minute intervals: stimulus 2, before administration of the regional anesthetic; stimulus 3 before incision; stimuli 4 and 5 during the early portions of the surgical procedure. Stimulus 6 evaluated memory after completion of the operation and was presented when the patient was ready to be dismissed from the recovery room. The visual card was shown immediately before stimulus 2. Table 3 shows actual mean time relative to the test drug that the stim-

uli were presented to each of the groups. Analyses of variance revealed no statistically significant differences in these times.

Instructions and Procedures.—Following the preanesthetic examination, volunteers were interviewed and given instructions by a research technician (experimenter 1). All were informed about the type of stimuli they might receive and instructed to try to remember as much as possible about the surgical events.

On the day of operation, a second research technician (experimenter 2) met the patient in the holding area, provided further instructions, placed the earphones, established a comfortable volume level, presented both the visual and auditory stimuli at the appropriate times, rated the patient for alertness at each stimulus presentation, and interviewed him on leaving the recovery room. Alertness at each stimulus presentation was rated on a 5-point scale, with the following descriptive range:

1. Highly alert
2. Alert
3. Drowsy
4. Light sleep
5. Deep sleep

Experimenter 1, without knowledge of tape assignments or alertness ratings, interviewed each patient approximately 24 hours after the operation. The interview included standard questions about surgical and recovery room events, a patient rating of the test drug, and measurement of recall and recognition of visual and auditory stimuli. For visual recognition, the dollar bill was presented along with 7 other familiar pictures (eg, postage stamps); for the auditory task, recognition was evaluated using a composite tape which, for each patient, consisted of the stimuli intermixed with 6 additional word pairs and 6 additional sounds. In both cases, the patient was asked to indicate if he recognized any of the stimuli as having been presented on the day of operation.

RESULTS

The frequency of *yes* (recall, recognition) and *no* (no recall, no recognition) responses of the 2 groups was compared by chi-square analysis. Summary of the recall and recognition data (table 3) indicates that both groups performed at a high level and did not differ in their memory of stimulus 1. Since this stimulus was presented before the test drug, the lack of difference suggests that lorazepam did not have a retrograde effect upon memory. All other group comparisons of recall and recognition, except one, achieved statistical significance, indicating that lorazepam affected memory within 20 minutes after IV administration and that, in general, this effect persisted throughout the total measurement period of more than 3 hours. Although there were some differences in actual scores, these findings were consistent for both the visual (dollar bill) and auditory (stimulus 2) stimuli, suggesting that the loss occurred with both modalities.

TABLE 3

Mean Time of Stimuli Relative to Test Drug (IV) and Percentage of Patients in the Lorazepam (n = 20) and Placebo (n = 19) Groups that Recalled and Recognized Each Stimulus

Stimulus			Time, min		Recall, %		Recognition, %	
Number	Type	Related events	Lorazepam	Placebo	Lorazepam	Placebo	Lorazepam	Placebo
1	Words	Predrug	−2.7	−3.3	90	89	95	100
—	—	IV drug	0	0	—	—	—	—
—	Picture	Prespinal	23.8	28.3	15	74*	25	100*
2	Sound	Prespinal	23.8	28.3	0	84*	50	100*
3	Words	Preincision	47.7	53.1	0	32†	10	89*
4	Sound	Intraoperative	67.7	72.6	0	68*	30	89*
5	Words	Intraoperative	86.5	92.9	10	42	15	100*
6	Sound	Leaving recovery room	217.3	190.4	15	68*	20	89*

*Difference between lorazepam and placebo groups significant at $p<0.01$.

†Difference between lorazepam and placebo groups significant at $p<0.05$.

Table 3 also illustrates that estimates of memory may vary as a function of both the type of stimuli and type of measurement. Recall, especially of words, was less reliable than recognition and may be a poorer estimate of memory in the complex surgical situation where even the placebo patient may be distracted by other, more relevant, events. In addition, the recognition scores appeared to be similar to those obtained for memory of relevant events (eg, entering OR, testing anesthesia with a needle, leaving recovery room). There were significant group differences in all chi-square comparisons ($df=1$) of memory for relevant operating-room events, with 89 to 100% of the placebo patients having a recall of these events as compared to only 28 to 50% of the lorazepam patients. Again, these differences persisted until the patient left the recovery room.

The effects obtained with alertness ratings were similar to those exhibited for memory. There were no group differences in the holding area (stimulus 1) before administration of the test drug, and patients generally were awake and lightly sedated ($\bar{x}=1.9$ for lorazepam and 1.7 for placebo). While ratings were not taken between stimuli 1 and 2, observation of patients suggests that the sedative effect of lorazepam began almost immediately after IV administration and that many were drowsy or fell asleep within 5 to 10 minutes.

Highly significant group differences were found for all measurements after administration of the test drug ($p<0.01$), beginning in the operating room with stimulus 2 ($\bar{x}=3.3$ for lorazepam and 1.8 for placebo) and continuing through recovery with stimulus 6 ($\bar{x}=2.6$ for lorazepam and 1.5 for placebo). During the interval from stimulus 2-5, 70 to 80% of the lorazepam patients were drowsy (rating 3) or asleep (ratings 4 and 5) and 40 to 55% were too sedated or disoriented to repeat the stimuli when they were presented. This did not appear to affect the overall conclusions about lorazepam and memory, since further analysis suggested that the loss in recall and recognition was similar, whether or not the stimulus could be repeated during the operation.

Consistent with but more important than the alertness rating results was the finding that significantly more lorazepam patients (n=6) than placebo patients (n=0) were considered to be oversedated ($\chi^2=4.62$, $df=1$, $p<0.05$). Five of these lorazepam patients were rated unsatisfactory by the anesthesiologist, while the sixth was rated satisfactory but considered to be borderline. In all these cases, the patient was judged to be so deeply sedated that it was difficult to judge the level of regional anesthesia. None responded to verbal commands when tested for sensory levels. Four responded only with general reflex movements, while 2 were completely obtunded and gave no response at all. Even though these patients were markedly sedated, respirations were deep and adequate, none requiring ventilatory assistance.

Lorazepam incidentally appeared in these studies to have little effect upon the cardiovascular system (table 4). Measurements of pulse and blood pressure taken before administration of the test drug, upon entering the operating room, after the regional anesthesia, and in the recovery area indicated no significant differences between the 2 groups.

Patient ratings of the test drugs indicated a group difference ($\chi^2=9.84$, $df=3$, $p<0.05$), with all lorazepam patients rating the premedication as excellent or good as compared to 74% for the placebo. Two (10%) of the placebo patients rated the test medication as only fair, and 3 (16%) considered it to be poor.

Numerous post-hoc evaluations of the lorazepam data attempted to determine the factors that might differentiate between the sedated and oversedated patients. While

TABLE 4
Mean Values for Blood Pressure and Pulse Rate

Measurement	Systolic (mmHg)		Diastolic (mmHg)		Pulse rate (per/min)	
	Lorazepam	Placebo	Lorazepam	Placebo	Lorazepam	Placebo
Predrug	127.7	129.2	80.3	79.5	79.4	76.7
Enter operating room	128.8	135.0	78.8	81.8	80.4	78.8
Regional	124.8	130.0	72.5	77.4	81.5	80.7
Recovery	121.8	122.2	72.7	73.8	76.4	72.9

weight suggested a possible trend, the only significant factor was age ($\chi^2=5.95$, $df=1$, $p<.0.05$). All 6 of the patients judged as oversedated were among the 10 patients between the ages of 46 to 63 years, while this condition was not found in any of the 10 patients between ages 23 to 26. Further comparisons of age within the lorazepam group suggested differences only for alertness ratings, with no differences in memory, body weight, blood pressure, pulse, pulse pressure, length of operation, or length of stay in the recovery room.

DISCUSSION

The combination of meperidine (50 mg) IM and lorazepam (4 mg) IV led to heavier sedation and less recall and recognition of events and stimuli than meperidine IM with placebo. These differences persisted throughout the whole measurement period of approximately 3 hours and, for at least some patients, may have continued into the night of surgery. These suggestions of long-lasting effects are consistent with previous reports on the use of lorazepam as a premedicant[7,8] and suggest that its effects are more persistent than those noted with even higher doses of diazepam.[2,5,6] In addition to these positive findings are the suggestions that respiration, blood pressure, and pulse were not differentially affected by lorazepam and that there were no adverse changes even when patients were considered to be oversedated. These suggestions are consistent with previous reports on the use of IM lorazepam.[8]

The finding of excessive sedation with patients over age 40 was not predicted from either our own preliminary pilot work with 4 mg (unpublished) or from a study by Heisterkamp and Cohen,[7] which used 5 mg IV lorazepam as a premedicant for regional anesthesia. However, it is difficult to make comparisons across these studies, since the mean age of patients in our pilot project was 26.2 years (n=5) and since Heisterkamp and Cohen[7] did not provide the ages of their patients (n=5).

In view of the current findings and the lack of comparable data, we performed 2 additional pilot evaluations in patients 40 years of age or over, to (a) determine whether a lower fixed dose might be adequate, and (b) evaluate the use of a weight-related dose. The first pilot study evaluated 2 mg (n=3), 3 mg (n=4), and 4 mg (n=4), but was discontinued when the 2-mg dose did not appear to provide sufficient sedation and 1 patient in each of the other groups (3 and 4 mg) was oversedated. In the second study (n=9), using a dose of .044 mg/kg rounded to the nearest 0.5 mg, 2 patients were also considered to be oversedated.

While there were not enough cases for statistical analysis of these pilot studies, one may speculate from the combined data that the desirable dose level may be close to .044 mg/kg. Unsatisfactory ratings were given to 2 of 4 patients who received more than .048 mg/kg, 2 out of 8 patients who received between .042 to .048 mg/kg, and 0 out of 8 patients with lower dose levels, suggesting that values above .044 mg/kg may increase the chances of oversedation.

On the other hand, values below .044 mg/kg may have a reduced effect upon both sedation and memory. None of the 9 patients receiving doses above .044 mg/kg recalled any stimuli, while of the 11 receiving less than this value, 4 recalled stimulus 2. Two of these latter patients also recalled 1 or more later stimuli. This suggests that limits around .044 mg/kg may be very narrow for individuals above age 40 and, more importantly, indicates the need for additional research to establish a useful dose level for all age groups. Studies are needed both with and without the use of meperidine, since the finding of excessive sedation in older patients may be due to the combined effects of meperidine with lorazepam.

In conclusion, this study indicates that lorazepam may be useful and safe to use as a premedicant, especially when the surgical procedure is prolonged, and that it may be readily accepted by patients. Although the drug may have no retrograde effect upon memory, and even though patients may appear to be awake, it significantly reduces recall and recognition of events for as long as 3 hours after a single IV injection. However, because of its powerful and persistent sedative effects, further research is necessary to determine useful dose levels and to establish the possible drug interactions between this benzodiazepine tranquilizer and narcotic analgesics.

ACKNOWLEDGMENT

The authors wish to thank Marilyn Baker and Gary Kline of the Psychology Service, Veterans Administration Hospital, for their valuable assistance in all phases of this study.

REFERENCES

1. Cherkin A, Harroun P: Anesthesia and memory processes. Anesthesiology 34:469-474, 1971

2. Dundee JW, Pandit SK: Anterograde amnesic effects of pethidine, hyoscine and diazepam in adults. Br J Pharmacol 44:140-144, 1972

3. Pandit SK, Dundee JW: Preoperative amnesia. Anesthesiology 25:493-499, 1970

4. Pandit SK, Dundee JW, Keilty SR: Amnesia studies with intravenous premedication. Anesthesiology 26:421-428, 1971

5. Clarke PRF, Eccersley PS, Frisby JP, et al: The amnesic effect of diazepam (Valium). Br J Anaesth 42:690-697, 1970

6. Hendrix GH: Intravenous use of diazepam in cardioversion. South Med J 62:483-484, 1969

7. Heisterkamp DV, Cohen PJ: The effect of intravenous premedication with lorazepam (Ativan), pentobarbitone or diazepam on recall. Br J Anaesth 47:79-81, 1975

8. Knapp RB, Fierro L: Evaluation of the cardiopulmonary safety and effects of lorazepam as a premedicant. Anesth & Analg 53:122-124, 1974

9. Wilson J, Ellis FR: Oral premedication with lorazepam (Ativan): a comparison with heptabarbitone (Medomin) and diazepam (Valium). Br J Anaesth 45:738-744, 1973

ANTIEMETIC EFFECT OF THC Oral delta-9-tetrahydrocannabinol (THC) was compared with a placebo as an antiemetic for nausea and vomiting following cancer chemotherapeutic drugs. Oral THC (10 mg/m^2) was an effective antiemetic in 14 of 20 courses while the placebo was ineffective in all instances. The lack of THC effect in some patients may be related to failure of gastrointestinal absorption. No patient vomited while experiencing a "high" from THC. Although somnolence often occurred with this THC dose, a significant curtailment of activities was infrequent. Toxicity (fear, panic, hallucinations) occurred in only two patients, both after three THC doses of 20 mg. *(Sallan SE, Zinberg NE, Frei E: Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. NEJM 293:795-797, 1975)*

Analysis of Tasks and Human Factors in Anesthesia for Coronary-Artery Bypass

PETER J. KENNEDY, MS*
ALFRED FEINGOLD, MD†
EARL L. WIENER, PhD‡
RONALD S. HOSEK, PhD§
Miami, Florida‖

A comprehensive task analysis of the anesthetist's activities during coronary-artery bypass procedures was carried out using time-lapse cinematography. This film was analyzed frame by frame to detect types of activities and the proportion of time spent on each. Link analysis was used to reveal recurring sequences of activities. Of the 9 activity categories, the anesthetist spends the greatest portion of time observing the patient and scanning the entire operative and monitoring field. Ten to 15% of the time is spent logging data on the anesthetic record. The challenge for the anesthetist is to optimize his performance, and those under his direction, in the face of the changing workload resulting from variations in patients' conditions. Use of an automated monitoring system that charts patient vital signs would allow the anesthetist to apportion this time among other tasks.

THE functions of anesthetists are subject to extreme fluctuations. A task analysis during coronary-artery bypass, employing time-lapse cinematography, was undertaken to reveal the extent to which total activity and particular duties fluctuate during anesthesia.

METHODS

The time-lapse cinematography used the following equipment: 16 mm camera (Bell and Howell, model 70-DR) equipped with a custom-made synchronous motor and Geneva drive (Lafayette Instruments Company, model 5406); Kodak Ektachrome 7242 emulsion EF type B 449, ASA 125, which permitted exposure under ambient illumination. The camera equipment was located outside a window of the operating room, as unobtrusively as possible.

Preliminary studies showed that the anesthetist is involved in virtually no activities completed in less than 2 seconds and, therefore, an interframe interval of 2 seconds was acceptable.[1] Detailed activity was subjected to frame-by-frame analysis.

Transcription of the data from film to workable form was facilitated by entering the data directly into a computer keyboard (PDP-12) while viewing the films. The computer program then performed a number of calculations including the tally of elapsed time, man-minutes per activity code, and link analysis. The rate at which the films were reviewed was approximately 2000

*Registered Professional Engineer, IBM, Boca Raton, Florida.

†Assistant Professor of Anesthesiology.

‡Professor of Industrial Engineering and Management Sciences.

§Assistant Professor of Biomedical Engineering.

‖Departments of Biomedical Engineering and Management Sciences, University of Miami, Department of Anesthesiology, University of Miami School of Medicine, Miami, Florida 33152.

Paper received: 5/9/75
Accepted for publication: 10/1/75

frames (1 hour's surgical operative time) in an 8-hour day. Initial analysis of the films established 13 categories of anesthetists' activities[2]; this was subsequently reduced to 9 categories (table). In 5 of these, the anesthetist's attention is directed toward, in 3, away from, and in 1, both toward and away from the patient-surgical field.

Three elective coronary-bypass procedures lasting 6, 8, and 9 hours were studied in the context of a teaching hospital where surgical anesthesia and operations were performed by residents and faculty. The procedures were divided into 3 phases: (1) prepump, wherein the patient is prepared, anesthesia is induced, thoracotomy is performed, and the pump tubing is connected; (2) on-pump, during which the respirator is shut off and circulatory bypass is effected; and (3) post-pump, during which the patient's heart is defibrillated and the surgical procedure is completed.

RESULTS

Figure 1 is an overview of the activities for case 1. The abscissa represents the elapsed time in hours. The ordinate scale is

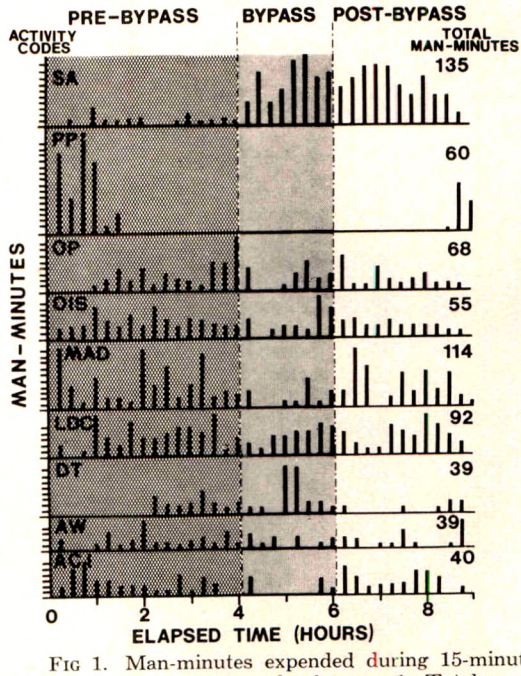


FIG 1. Man-minutes expended during 15-minute intervals on 9 activity codes for case 1. Total man-minutes is the sum of the man-minutes expended on an activity code. Symbols are defined in the table.

TABLE
Activity-Code Symbols

Symbol	Description	Attention*
ACI	Adjust or calibrate instrument (respirator, heating blanket, IV)	T & A
AW	Arrange equipment (instruments, table)	A
DT	Data transfer: anesthetist communicates or gestures to another person	A
LDC	Log data on anesthetic record or read chart	A
MAD	Mix or administer drugs	T
OIS	Observe oscilloscope or other monitor	T
OP	Observe patient (skin color, surgical field, etc.)	T
PP	Prepare patient (place ECG leads, BP, transducers, etc.)	T
SA	Scan area (attention not directed to any instruments or display but scanning entire field)	T

*"T" indicates that the anesthetist's attention is directed *toward* the patient-surgical field. "A" indicates that the anesthetist's attention is directed *away* from the patient-surgical field.

repeated once for each activity code and represents the man-minutes expended during 15-minute intervals on that activity code. The number at the extreme right of each activity represents the total time in man-minutes for that activity. The sum of the total man-minutes for each activity code agreed closely with or exceeded the elapsed time.

At the beginning of the procedure, the anesthetist attached monitors, induced anesthesia, and intubated the patient; this is reflected (fig 1) by an initial peak of the activity code, prepare patient (PP). At the end of the case, another peak of PP occurs, indicating the preparations prior to transporting the patient to the postsurgical recovery unit. During bypass, some activities drop to a low level. The principal exceptions to this appear to be scan area (SA), and data transfer (DT).

Figure 2 summarizes the percent of the anesthetist's time expended on each activity code for the 3 cases. This summary is arranged in order of increasing time expended.

Sequences of activities which recur throughout the procedure were revealed by link analyses. A 9 x 9 matrix of the present

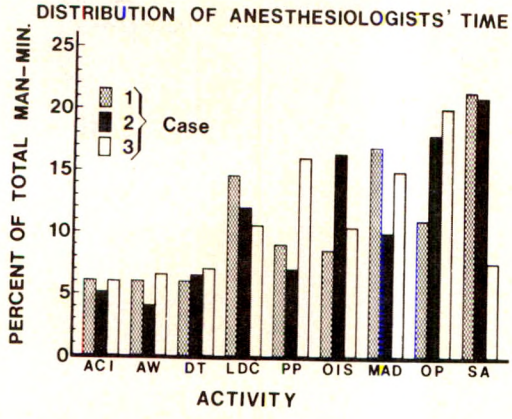


FIG 2. Percent distribution of anesthetist's time for the 3 cases. Symbols are defined in the table.

activity and the next activity was constructed. By dividing each present activity entry by the total of the corresponding present activity column and multiplying by 100, the table is normalized. For example, logging data (LDC) follows observing monitors (OIS) 51% of the time. If the present activity is OIS, there is a 9% probability that the next activity will be to observe patient (OP).

DISCUSSION

Few studies have applied quantitative measures to obtain data that can be used to improve the human factors in the practice of anesthesiology. Photographic time studies were pioneered by Gilbreth,[3] who proposed standards for some procedures. More recently, Drui and associates[4] used time-lapse cinematography to study 8 cases, including one 10-hour cardiac surgical procedure, for a total of 26 hours of study. Using 24 separate activity codes, they found that the largest amount of time was spent in filling out the anesthetic record and that 46% of the anesthetist's time was spent looking away from the patient-surgical field.

Our data support many of their observations and conclusions. Figure 2 shows that the anesthetist spends 8 to 22% of his time scanning the area (SA), 11 to 22% observing the patient (OP), 10 to 17% mixing or administering drugs (MAD), 8 to 17% observing monitors (OIS), 7 to 16% preparing the patient for anesthesia and transfer (PP), 10 to 15% logging data or reading chart (LDC). The time spent looking away from the patient-surgical field on other essential tasks may include the categories LDC, DT, AW, ACI, and amounts to 28 to 33% of the total man-minutes.

The anesthetist's primary tasks are to observe the patient, observe monitoring equipment, and continuously review his options of drugs and dosage. Superimposed upon these are a variety of secondary tasks, such as fluid replacement, preparation of supplies, and updating the clinical record.

Like Drui's group, we found the placement of equipment and displays in the operating rooms was haphazard. In two institutions, the multichannel oscilloscope was behind the anesthetist, requiring a body movement for the OP→OIS sequence. Although this location is convenient for the surgeons, relocation of the oscilloscope would reduce body movements of the anesthetist.

Link analysis showed that OIS, SA, and MAD are followed by logging data (LDC) 51%, 46% and 37% respectively. OIS follows LDC, OP, MAD, and PP 43%, 33%, 34% and 33% respectively. These data further emphasize the importance of proper arrangement of the equipment in the patient-surgical field.

Our results show that periodic transcription of patient data to the anesthetic record (LDC) requires 10 to 15% of the anesthetist's time. An automated system for charting the patient's vital signs would allow the apportionment of this time among the remaining tasks. In addition to logging vital signs, a computerized system could produce a more complete and accurate record than a manual system. Additional information available from the ECG could be computed, displayed, and recorded. The computer-produced record might also provide useful information for postoperative studies.[4]

Our observations suggest that any automated system should include a properly placed oscilloscope display. Additional functions should be added to the display to show trends and allow a comprehensive clinical picture of the patient's status with only limited eye movement by the anesthetist.

Improved patient care can follow if human-factors and systems specialists study anesthetic procedures and identify error-producing aspects resulting from the interaction between the anesthetist and his equipment. The collection and analysis of design-induced errors, perhaps using the method described by Fitts and Jones[5] to study design-induced pilot errors, could lead to the identification of recurring problems, which could then be designed out of the anesthesia man-machine systems.

REFERENCES

1. Wiener EL: Time-lapse cinematography. Indust Photog 17:28-30, 1968

2. Kennedy PJ: An activity analysis method and feasibility study of digital computer application in surgical anesthesiology. Masters Thesis, University of Miami, June 1974

3. Gilbreth FB: Motion study in surgery. Can J Med Surg 40:22-31, 1916

4. Drui AB, Behm RJ, Martin WE: Predesign investigation of the anesthesia operation environment. Anesth & Analg 52:584-591, 1973

5. Fitts PM, Jones RE: Analysis of factors contributing to 460 "pilot-error" experiences in operating aircraft controls. Selected Papers on Human Factors in the Design and Use of Control Systems. Edited by HW Sinaiko. New York, Dover Publications, Inc, 1961

AWAKE DURING OPERATION Awareness during anesthesia and operation may result in a traumatic neurotic syndrome. The authors describe such a syndrome in six patients characterized by 1) recurrent nightmares, 2) irritability, 3) a preoccupation with death, and 4) reluctance to describe symptoms to physicians for fear they would be misinterpreted. In all six cases a direct explanation to the patient that they indeed were "awake" during the operation served as a dramatic cure. The incidence of such occurrences may be underestimated due to patient reluctance to discuss their symptoms. *(Blacher RS: On awakening paralyzed during surgery. A syndrome of traumatic neurosis. JAMA 234:67-68, 1975)*

Anesthetic Considerations for Pericardectomy in Uremic Pericardial Effusion

HALAPPA N. KONCHIGERI, MD*
SIDNEY LEVITSKY, MD†
Chicago, Illinois‡

Fifteen patients with impending uremic cardiac tamponade underwent either anterior pericardectomy or pericardiostomy under general anesthesia. Anesthetic agents and technics were selected in the light of physiopathologic derangements involving fluids and electrolyte balance, excretory and cardiovascular disturbances, and pharmacodynamics. Anesthesia was induced with diazepam and maintained with N_2O-O_2 (70:30) and fentanyl. Pancuronium was used for muscle relaxation. Adequate preoperative assessment of patient, careful monitoring of vital signs, maintenance of the critical balance of fluid and blood replacement, and selection of anesthetic agents for minimal depression of vital multiorgan systems provided excellent results. No postanesthetic morbidity or mortality occurred.

ALTHOUGH pericarditis associated with uremia has been known since 1836,[1] cardiac tamponade in this condition was first documented only in 1956.[2] This potentially dangerous condition has been reported in patients both before and after beginning maintenance hemodialysis. Cardiac tamponade has been observed in 2.6 to 6% of patients in renal failure and 15 to 55% of uremic pericarditis cases.[3] The increasing incidence is considered due to the prolongation of life of uremic patients by maintenance dialysis.

The recommended treatment for uremic pericardial effusion with tamponade is aggressive dialysis, repeated pericardiocentesis, creation of a pericardial window, or partial pericardectomy. Based on current data, partial pericardectomy has been strongly advocated as the definitive treatment of uremic pericardial tamponade.[4]

In the anesthetic management, the anesthesiologist is faced with the basic problems of chronic renal failure[5] compounded by the changes in cardiovascular hemodynamics brought by the uremic cardiac tamponade. This presentation describes special anesthetic problems and our experience in the anesthetic management for either pericardiostomy or anterior pericardectomy (phrenic-to-phrenic) in patients with uremic pericardial effusion and constriction.

MATERIALS AND METHODS

Fifteen patients with uremic pericardial effusion and clinical signs of impending tamponade underwent either anterior pericardectomy (12 patients) or pericardiostomy (3 patients) under general anesthesia. Patients, 10 males and 5 females, ranged in age from 15 to 66 years (average 31). All except 1 (class IV) were of ASA physical status III.

Preoperative Evaluation.—Most patients were underweight, undernourished, and mentally depressed. Predominant physical

*Assistant Professor of Anesthesiology.
†Associate Professor of Surgery.
‡Departments of Anesthesiology and Cardio-Thoracic Surgery, Abraham Lincoln School of Medicine, University of Illinois Hospital at the Medical Center, Chicago, Illinois 60612.

Paper received: 4/28/75
Accepted for publication: 9/28/75

TABLE 1
Hematologic and Biochemical Data

Normal	Results	
	Mean	Range
Hb (gm): 14-18 (M); 12-16 (F)	7.57	4.5-12.0
Hct (%): 42-52 (M); 37-47 (F)	24.34	14.5-36.0
K^+ (mEq/L): 4.4 ± 0.9	4.24	3.0-5.4
Na^+ (mEq/L): 142 ± 7	139.3	134.0-154.0
Cl^- (mEq/L): 103 ± 5	101.0	92.0-110.0
Ca^{++} (mg %): 5 ± 0.5	4.1	4.0-4.2
P (mg %): 2-4.5	2.92	2.8-3.1
BUN (mg %): 14 ± 6	41.3	16.0-52.0
Creatinine (mg %): 1 ± 0.5	7.7	2.3-12.0
Glucose (mg %): 87 ± 22	102.3	76.0-145.0
Total protein (gm): 7.1 ± 1.1	4.7	3.2-5.9

findings were tachypnea (>25/min), tachycardia (>100/min), temperature elevation of 1 to 3° F above normal, elevation of central venous pressure (CVP) (>15 cm H_2O), and mild to moderate degrees of hypertension. There was increased cardiac dullness on percussion and bilateral basal moist rales on auscultation in the majority. Patients were receiving multiple medications, including methyldopa, digitalis, furosemide, azothioprine, prednisone, antibiotics, and supplemented iron therapy.

Laboratory Data.—Preoperative hematologic and biochemical data (table 1) showed polymorphonuclear leukocytosis in 12 patients. Platelet count (carried out in 10 patients) was reportedly normal. Chest roentgenography revealed progressive cardiomegaly in all patients. Electrocardiographic abnormalities included left ventricular hypertrophy with strain (5 patients), nonspecific ST-T wave changes (2 patients), junctional rhythm (2 patients), atrial flutter with 3-to-1 block (1 patient), and sinus tachycardia (several patients).

All patients were on regular maintenance hemodialysis, 2 or 3 times a week, before hospitalization. Intensive medical management of pericardial effusion involved daily hemodialysis and pericardiocentesis. Surgical intervention was considered necessary only in those patients who exhibited radiographic evidence of enlarging cardiac silhouette, accompanied by: (1) signs of cardiac embarrassment (arrhythmias and hypotension), (2) elevated CVP and/or paradoxical pulse pressure of 15 to 20 torr, (3) negative response to aggressive hemodialysis, and (4) echocardiographic evidence of increased accumulation of pericardial fluid.

Premedication.—Five patients received 5 to 10 mg of diazepam IM, approximately 1 hour before anesthesia, while the remainder received no premedication.

Anesthetic Management.—Baseline readings of vital signs (temperature, respiratory rate, pulse rate, blood pressure, ECG and CVP) were recorded. The usual sterile surgical preparation and draping were carried out while the patient received O_2 by face mask before induction of anesthesia.

Anesthesia was induced with diazepam, administered in incremental doses of 5 mg (total dose 10 to 25 mg) until optimal sedation was reached without untoward effect on vital signs. Pancuronium (0.1 mg/kg) was administered to facilitate endotracheal intubation. Anesthesia was maintained with 70% N_2O in O_2 and supplemented with minimal doses of fentanyl. Ventilation was controlled in all patients throughout the surgical procedure, and arterial blood gas was measured intraoperatively in 8. Midline sternal splitting incision was used for thoracotomy in patients scheduled for anterior-pericardiectomy, which involved removal of anterior pericardium between the phrenic nerves as well as excision of the pericardial reflections around the venae cavae, and a subxiphoid incision was used for pericardiostomy.

At the termination of the procedure, the residual effect of pancuronium was reversed by administering 5 mg of prostigmine and 1.2 mg of atropine in a premixed solution. Patients were extubated either in the operating room or in the cardiac surgical intensive care unit after assessment of vital signs and adequacy of ventilation.

Intraoperative Monitoring.—In addition to the usual parameters (temperature, pulse, respiration, blood pressure, and tidal volume), CVP was measured in 6 patients, and intraarterial blood pressure, by placement of a catheter in the dorsalis pedis artery, in 4 patients.

Intravenous Fluids.—Patients received 200 to 1400 ml (average 680 ml) of 0.45%

TABLE 2
Pulse-Rate and Blood-Pressure Changes During Anesthesia and Recovery

	Pulse (Mean ± SD)	Blood pressure (Mean ± SD)	
		Systolic	Diastolic
Preinduction	101 ± 13	134 ± 29	81 ± 12
Induction	102 ± 13	142 ± 29	83 ± 16
Maintenance	107 ± 10	142 ± 25	85 ± 10
Recovery	99 ± 9	139 ± 21	83 ± 7

None of the parameters measured were statistically significant at $p < 0.05$.

normal saline solution in 5% dextrose and/or lactated Ringer's solution in 5% dextrose solution to replace serosanguinous fluid loss. Ten patients were given 1 to 4 units of triple-washed red blood cells intraoperatively.

RESULTS

Duration of the surgical procedure ranged between 70 and 300 minutes (average 143 minutes). Variations in either heart rate or blood pressure during anesthetic induction, maintenance, or recovery were not statistically significant (table 2) except in 1 patient, in whom there was a transient bradycardia (heart rate 50 to 55/min) during cardiac manipulation; this was promptly treated with IV administration of atropine. During dissection of a thick epicardial peel, a second patient developed premature ventricular contractions (PVCs) of 2 to 5/min; intervals of rest during the procedure improved the cardiac rhythm without the need for further therapy. Central venous pressure decreased by 3 to 10 cm H_2O as the chest and pericardial sac were opened. Average intraoperative blood-gas measurements were: Pao_2, 121 torr (111 to 150); $Paco_2$, 32.2 torr (27 to 38); pH, 7.49 (7.41 to 7.53); HCO_3, 24.9 (19 to 28).

Anesthesia provided highly satisfactory operating conditions, and all patients showed rapid recovery, complete amnesia, and a benign postanesthetic course. No postoperative mortality or morbidity was related to the anesthetic management.

Echocardiography.—Ultrasound scanning has been shown to be accurate, safe, and reliable for detecting pericardial effusion, and can be conducted at the bedside in a few minutes without patient discomfort.[6] Echocardiography is based on a simple principle: When ultrasound, passing through an acoustically uniform medium, reaches the interface with a medium of different acoustic impedance, some of the waves will be reflected back (echoes) to the transducer, while the remainder of the energy is transmitted into the second medium.[7] When an ultrasound transducer is placed along the left sternal border in the 4th or 5th intercostal space and facing posterolaterally, the ultrasonic beam will traverse the anterior chest wall and various structures of the heart to the posterior mediastinum and lung. Reflected ultrasonic energy (echoes) from the different media are recorded on the self-developing film of an ultrasonoscope. Pericardial fluid is recorded as echo-free space between the posterior left ventricular epicardium and the posterior pericardium. Anterior fluid is seen as a similar echo-free space between the anterior right ventricular wall and the anterior chest wall.[6]

DISCUSSION

Patients with uremic pericardial tamponade present complex homeostatic disturbances involving multiorgan systems. Chronic renal failure is associated with severe anemia, hypoproteinemia, chronic azotemia, and electrolyte disturbances. Although biochemical disturbances can be largely corrected by hemodialysis, emergency surgical procedure may require anesthetic administration in a patient with extreme biochemical disturbances. Decreased resistance and increased susceptibility to infection necessitates a meticulous aseptic technic and, frequently, antibiotic administration. The possibility of interaction between medications (antibiotics, immunosuppressive and antihypertensive agents, digitalis, diuretics) and anesthetic agents must be considered.

A majority of such patients are hypertensive and have associated cardiomegaly, conduction defects, atherosclerotic vascular changes, and uremic cardiomyopathy. In addition, patients are susceptible to serous effusion in peritoneal, pleural, and pericardial cavities.

Pericardial effusion produces several major hemodynamic changes. Cardiac tamponade limits diastolic expansion of heart chambers, increases intraatrial, intraventricular, and pericardial pressures, and leads to decreased stroke volume and cardiac output.[8,9] Left ventricular function has been shown to be depressed by significant falls in ejection fraction and mean ejection rate.[9] Increased pressure in both atria is reflected in a marked rise in pulmonary and systemic

venous pressure. During cardiac tamponade, cardiac output can be increased by expansion of total blood volume at the expense of raised central venous pressure.[10] There is a decrease in coronary blood flow, while myocardial metabolic O_2 demand is greatly increased as a resultant of tachycardia. Coronary blood flow may be critically affected by changes in coronary vascular resistance, heart rate, arterial pressure, and cardiac output.[11]

In patients with cardiac tamponade, cardiac output is reduced and therefore requires increased venous filling pressure; hence, anesthetic agents causing marked depression either of myocardial contractility or peripheral vascular resistance (PVR) should be used with great caution.[12] Monitoring of the CVP assists greatly in maintaining adequate fluid administration. Also, because of the increased incidence of cardiac arrhythmias in patients with tamponade, ventilation and oxygenation should be well maintained. Increased intrathoracic pressure due to straining or coughing during induction, or to overly vigorous controlled ventilation, may result in further tamponade of the heart and intrathoracic veins, causing more hypotension.

Surgical removal of pericardium adherent to the pericardial surface may involve meticulous dissection, leading to considerable blood loss. Manipulation of the heart may greatly upset circulatory dynamics and precipitate hypotension or arrhythmias to the extent of ventricular fibrillation. Close monitoring of the cardiovascular system, gentleness in the surgical procedure, and adequate fluid and blood replacement are all essential for successful patient management.

Anesthetic Agents.—Reduced tolerance to the depressing effect of drugs and unstable cardiovascular dynamics in uremic pericardial tamponade warrant elimination or minimizing of the dosage of potent sedatives and narcotic premedicants. Thiopental induction is risky in patients with tamponade,[13] while diazepam has reportedly proved to be an excellent induction agent, with negligible cardiovascular depression, good anterograde amnesia,[14] and enhanced coronary blood flow through vasodilation.[15]

Halogenated inhalation anesthetics produce significant myocardial depression and peripheral vasodilation.[16,17] Although sympathomimetic effects of cyclopropane and diethyl ether are beneficial in maintaining PVR,[17] routine use of electric bone saws and other electric instrumentation excludes these agents from consideration. Ketamine, with no significant effect on PVR in patients with chronic renal failure,[18] may be considered useful. Morphine can produce significant decrease in systemic arterial resistance, vasodilation, peripheral pooling, and reduced venous return to the heart.[19] Administration of drugs with alpha or beta-blocking properties (droperidol, thorazine, phenoxybenzamine, phentolamine, propranolol) may be lethal in these patients. Because of the negligible effect of pancuronium on the cardiovascular system,[20] this drug was included in our anesthetic management.

Some authors[12] have advocated the technic of local infiltration and sedation for subxiphoid pericardiostomy. The disadvantages of this method are: (1) a large volume of local anesthetic may produce significant myocardial depression; (2) if the operative procedure is extensive, intraoperative anesthesia may be required; (3) synergistic action of the local and general anesthetic agents may produce cardiovascular depression.

Special attention must be paid in the proper care of A-V fistula in the arm, aseptic anesthetic technics, and adequate protection of pressure points on patient positioning. Radial artery and veins at the wrist are to be spared cannulation whenever possible, so that they can be used for a later A-V fistula. Dorsalis pedis artery puncture or cannulation can be used for obtaining blood-gas measurement and arterial pressure recordings.

In our present experience, adherence to the outlined principles of anesthetic management for pericardectomy has produced excellent results with no operative or anesthetic related mortality or morbidity.

ADDENDUM

Since this paper has been submitted for publication, pericardectomy has been done in three more patients with good results without any related sequelae.

ACKNOWLEDGMENT

The authors thank Doctors E. J. Bennett, S. Ramamurthy, C. B. Reddy, G. B. Schmidt, and E. M. Grundy for their valuable help in this study; and Miss Lourdes Q. Yolo for her secretarial help.

REFERENCES

1. Bright R: Tubular view of the morbid appearance in 100 cases connected with albuminous urine with observation. Guys Hosp Rep 1:380-400, 1836

2. Goodner CJ, Brown H: Report of two cases of cardiac tamponade in uremic pericarditis. JAMA 162:1459-1461, 1956

3. Singh S, Newmark K, Ishikawa I: Pericardectomy in uremia, treatment of choice for cardiac tamponade in chronic renal failure. JAMA 228: 1132-1135, 1974

4. Ghavamiam M, Gutch CF, Hughes RK, et al: Pericardial tamponade in chronic hemodialysis patients: treatment by pericardectomy. Arch Intern Med 131:249-253, 1973

5. Daughety MJ, Peters PC: Anesthesia for uremic patients, Clinical Anesthesia: Common and Uncommon Problems. Edited by MT Jenkins. Philadelphia, FA Davis Company, 1969, pp 336-344

6. Feigenbaum M: Echocardiographic diagnosis of pericardial effusion. Am J Cardiol 26:475-479, 1970

7. Silber EN, Katz LN: Heart Disease. New York, The Macmillan Company, 1975, chapter 18, pp 436-439

8. Fowler NO: Pericardial disease, The Heart, Arteries and Veins. Edited by JW Hurst, RB Logue. New York, The Blakiston Division, McGraw-Hill Book Company, 1966, p 846

9. Craig RJ, Whalen RE, Behar VS, et al: Pressure and volume changes of the left ventricle in acute pericardial tamponade. Am J Cardiol 22:65-74, 1968

10. Shabetai R, Fowler NO, Guntheroth WG: The hemodynamics of cardiac tamponade and constrictive pericarditis. Am J Cardiol 26:480-489, 1970

11. O'Rourke RA, Fischer DP, Escober EE, et al: Effect of acute pericardial tamponade in coronary blood flow. Am J Cardiol 212:549-552, 1967

12. Stanley TH, Weidauer HE: Anesthesia for the patient with cardiac tamponade. Anesth & Analg 52:110-114, 1973

13. Wylie WD, Churchill-Davidson HC: Anesthesia and cardiac disease, Practice of Anesthesia. Third edition. Chicago, Year Book Medical Publishers, chapter 24, pp 651-690

14. Dundee JW, Haslett WHK: The benzodiazepines: a review of their actions and uses relative to anaesthetic practice. Br J Anaesth 42: 217-234, 1970

15. Ikram H, Rubin AP, Jewkes RF: Effect of diazepam in myocardial blood flow of patients with and without coronary artery disease. Br Heart J 35:626-630, 1973

16. Brown BR, Crout JR: A comparative study of the effects of five general anesthetics on myocardial contractility. Anesthesiology 34:236-245, 1971

17. Eger EI II, Smith NT, Cullen DJ, et al: A comparison of cardiovascular effects of halothane, fluroxene, ether, and cyclopropane in man. Anesthesiology 34:25-41, 1971

18. Hobika G, Evers J, Mostert J, et al: Comparison of hemodynamic effects of glucagon and ketamine in patients with chronic renal failure. Anesthesiology 37:654-658, 1972

19. Stanley TH, Stanford W, Armstrong RG, et al: The effects of morphine anesthesia on blood requirements during and after valve replacement and coronary artery bypass. Ann Thorac Surg 17: 368-376, 1974

20. Harrison GA: Cardiovascular effects and some relaxant properties of four relaxants in patients about to undergo cardiac surgery. Br J Anaesth 44:485-493, 1972

Effect of Isoproterenol and Propranolol on Halothane MAC in Dogs

YASUMASA TANIFUJI, MD*
EDMOND I. EGER, II, MD†
San Francisco, California‡

To evaluate the effect of propranolol on anesthetic requirement, changes in minimum alveolar concentration (MAC) of halothane accompanying acute (2 and 10 mg/kg IV) and chronic (200 mg/day orally for 10 days) propranolol administration were determined in dogs. MAC did not change significantly in either case. Beta-adrenergic blockade was achieved with the 2 mg/kg propranolol dose, as indicated by abolition of the pulse rate increase in response to isoproterenol infusion. Isoproterenol itself did not alter MAC. Mean arterial pressure (MAP) and heart rate (HR) at any given level of alveolar halothane were the same before and after chronic propranolol administration. Acute IV administration of propranolol, especially at the 10 mg/kg dose, reduced MAP and increased HR only transiently.

PROPRANOLOL is used extensively for beta-adrenergic blockade in the treatment of angina,[1,2] and for hypertension.[3] It also has been used to treat arrhythmias during anesthesia. Several reports suggest that propranolol may be depressant in animals[4,5] and anxiolytic in man.[6,7] Propranolol may directly depress by a local-anesthetic-like action at the membrane.[8] These effects imply that a reduction in anesthetic requirement might result from propranolol administration.

Accordingly, we investigated whether propranolol given acutely or chronically might modify the minimum alveolar concentration (MAC) of halothane. At the same time, we determined whether the beta-adrenergic stimulator, isoproterenol, affected halothane MAC.

Cessation of propranolol treatment has been reported to cause a hazardous increase in myocardial ischemia. The argument for discontinuing propranolol prior to anesthesia is that continued beta-adrenergic blockade may make the cardiovascular system more susceptible to the depressant effects of anesthesia[9-12] or the stress of surgery.[13] To determine whether propranolol alters the cardiovascular response to anesthesia, blood pressure (BP) and heart rate (HR) were measured before and after propranolol administration at equal anesthetic doses.

MATERIAL AND METHODS

Healthy, unpremedicated dogs of various ages, breeds, sex, and weight (19.6 kg ± SE 1, range 14 to 22 kg) were anesthetized with halothane-O_2. A cuffed endotracheal tube was introduced without the use of muscle relaxants, and breathing was controlled with a volume-limited respirator. Intermittent end-tidal gas samples were obtained from the end of the endotracheal tube via a nylon

*Research Trainee.

†Professor.

‡Department of Anesthesia, University of California, San Francisco, California 94143.

This study was supported in part by the Foundation for Inservice Training and Welfare of the Private School Personnel in Japan and GM 15571-07.

Paper received: 7/10/75
Accepted for publication: 11/5/75

catheter. Halothane was analyzed with a Beckman LB-1 infrared analyzer. Esophageal temperature was maintained at 37.5 ± 1° C by heating pads and ice. MAC was determined as described previously.[14] All measurements were made after at least 15 minutes of a constant end-tidal halothane concentration.

Arterial blood was drawn via catheter from the femoral artery for Pao_2, $Paco_2$, and pH. $Paco_2$ was maintained at 25 ± 2 torr (SEM), a level which does not influence MAC.[15] Blood pressure, from the femoral artery, and HR were recorded on a Grass polygraph.

Acute Experiments.—After induction with halothane, control MAC was determined in 8 dogs. Isoproterenol (0.8 μg/ml) was administered as a continuous IV infusion. MAC again was measured at an HR increased to 80% above control levels by adjustment of the isoproterenol infusion. Twelve ± 2 minutes after measurement of this "isoproterenol MAC," propranolol (2 mg/kg) was injected. To determine whether the propranolol had completely blocked beta-receptors, isoproterenol was infused for 5 minutes at the same speed as had previously doubled the HR, which now remained unchanged by the isoproterenol. After this confirmation, the propranolol MAC was determined. Finally, a large propranolol dose (10 mg/kg) was injected 106 ± 15 minutes after the 2 mg/kg propranolol injection. Following this, we again measured MAC.

Chronic Experiments.—Since propranolol commonly is administered chronically, we also examined whether chronic administration differed from acute administration in its effect on MAC. Halothane MAC was determined in 6 normal unmedicated dogs. Propranolol (200 mg) was then administered orally each day (mean 11.6 mg/kg/day: range 9.5 to 16.7 mg/kg/day) for about 10 days (range 8 to 11 days), after which halothane MAC was redetermined. Following the determination of this chronic propranolol MAC, we examined whether such chronic oral administration blocked HR response to the isoproterenol infusion (0.8 μg/kg) previously found to double HR. In both acute and chronic experiments, each MAC was corrected to a body temperature of 37° C.[16] Results were analyzed for statistical significance by paired analysis with Student's *t*-test. A p value of less than 0.05 was accepted as significant.

RESULTS

Acute Experiments.—Isoproterenol infusion initially decreased BP by 22% (table), but by 10 minutes after the start of infusion, pressure had returned to control values. The 2 mg/kg propranolol injection did not induce a fall in BP. HR transiently decreased 27%, but rapidly returned to control values (table). Isoproterenol infusion following propranolol did not increase pulse rate. With the larger dose of propranolol (10 mg/kg), BP initially decreased and HR increased (table), these values returning to or toward control levels in about 20 minutes (fig 1). MAC was not affected significantly by any treatment (fig 2, table).

Chronic Experiments.—After oral propranolol administration (200 mg/day) for 10 days, BP values at any given level of halothane anesthesia were nearly the same as prior to propranolol administration, and HR changed little (fig 3). Incomplete atrioventricular block was observed in 1 dog

TABLE

Mean Arterial Pressure and Heart Rate Changes After Isoproterenol or Propranolol

			Propranolol 2 mg/kg		Propranolol 10 mg/kg	
	Control (N = 8)	After 5 minutes of isoproterenol infusion (N = 8)	After 5 minutes (N = 7)	After 5 minutes of isoproterenol infusion (N = 6)	After 5 minutes (N = 5)	After 20 minutes (N = 5)
Mean arterial pressure, torr	86 ± 4.3	67 ± 6.3	87 ± 5.6	85 ± 5.0	71 ± 7.5	77 ± 7.7
(% of control)	(100)	(78 ± 5)	(106 ± 6)	(103 ± 5)	(89 ± 7)	(98 ± 7)
Heart rate	84 ± 4.6	148 ± 4.5	93 ± 5.7	92 ± 8.5	106 ± 7.5	98 ± 4.9
(% of control)	(100)	(179 ± 10)	(100 ± 8)	(112 ± 11)	(124 ± 8)	(116 ± 8)
Halothane MAC*	0.95 ± 0.07	0.98 ± 0.05	0.93 ± 0.05		0.99 ± 0.06	

*Absolute % ± SEM. N = 8 for all except propranolol 10 mg/kg, where N = 6.

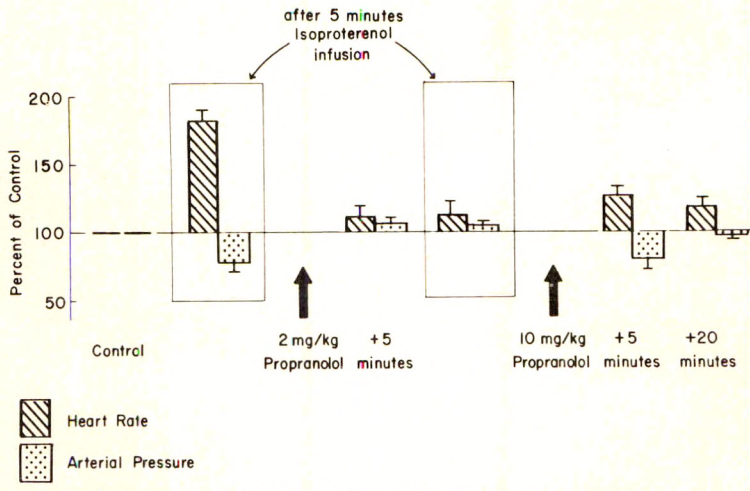


FIG 1. Heart rate and mean arterial pressure in acute experiments are given as a percent of values obtained during halothane anesthesia prior to isoproterenol or propranolol injection. Heart rate and pressure changes following propranolol on the average were small and transient. Before, but not after propranolol injection, isoproterenol increased heart rate and decreased blood pressure. For number of animals at each point see the table.

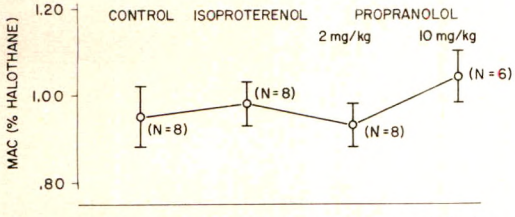


FIG 2. Neither an IV isoproterenol infusion sufficient to double the heart rate nor 2 or 10 mg/kg IV injection of propranolol altered MAC for halothane in acute experiments. MAC values are given as average percent halothane ± SEM.

given the largest dose of propranolol (16.7 mg/kg/day). Another dog showed incomplete beta-blockade, indicated by its response to isoproterenol. No significant changes in MAC were seen. Halothane MAC was 0.99 ± 0.08% before chronic propranolol administration and 1.08 ± 0.08% after.

DISCUSSION

Propranolol given either acutely or chronically did not make the average dog more susceptible to halothane-induced hypotension or bradycardia (figs 1 and 3). Thus, our data do not support the argument that propranolol must be discontinued before halothane anesthesia. However, such data may not be immediately extrapolated to patients, particularly those with heart disease conferring limited cardiovascular reserve.

Moreover, we did not explore the interaction of propranolol on myocardial contractility or cardiac output. It should be noted that the larger doses of propranolol given IV over a period of 3 to 4 minutes did cause a mild, transient hypotension and tachycardia during halothane anesthesia. Tachycardia at this time may have resulted

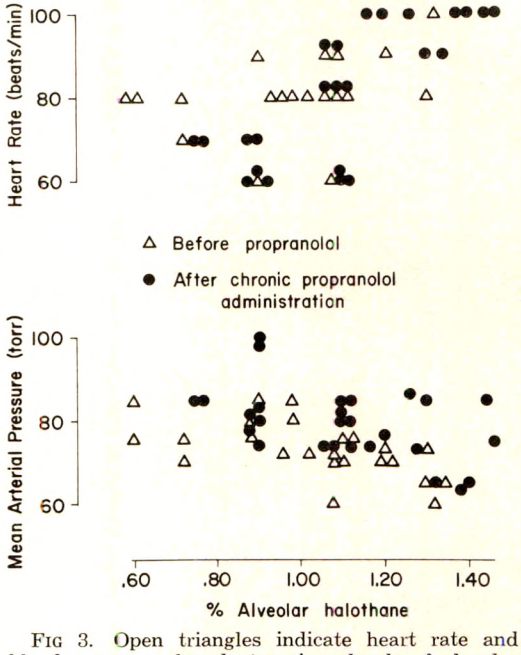


FIG 3. Open triangles indicate heart rate and blood pressures found at various levels of alveolar halothane in 6 unmedicated dogs. Closed circles indicate heart rate and pressure found after oral administration of 200 mg/day of propranolol for 10 days. It is apparent that propranolol did not significantly alter response of these variables to depressant effect of these levels of halothane.

from incomplete beta-sympathetic blockade in the presence of baroreceptor stimulation due to the hypotension. A possibility we believe unlikely is that reduced sympathetic activity may have caused tachycardia associated with transient acute cardiac dilatation.

Our findings that neither acute nor chronic administration of propranolol alters halothane MAC appear to conflict with reports of depression following propranolol administration.[4,5] They also appear to conflict with studies suggesting synergistic action between propranolol and other CNS depressants.[17,18] However, the doses of propranolol used in these other studies were 10 times larger than we used. In agreement with our work, Lader and Tyrer[19] found in normal human subjects that no central effects of propranolol were produced by 120-mg doses given acutely. They pointed out that the dosage in most experimental studies was much greater than used therapeutically. Also, since the longer the duration and higher the dosage of propranolol therapy, the higher the incidence of depression,[7] it is possible that our chronic experiments (10 days) were too short in duration to reveal the true depressant effect of propranolol.

Isoproterenol not having been reported to enter the CNS in significant quantities, it is hardly surprising that it did not affect MAC. In contrast, propranolol readily crosses the blood-brain barrier,[20] causes inhibition of the stimulatory effect of catecholamines on carbohydrate and lipid metabolism,[21-23] but does not alter brain noradrenaline after acute or chronic administration.[24] This uncertainty regarding the effect of propranolol on cerebral catecholamines prohibits any prediction of effect based on the known correlation between central amine reduction and MAC,[25] and indeed, although propranolol increases sleeping time in rats and mice following chloral-hydrate administration, this effect is not correlated with changes in brain amine concentrations.[24]

ACKNOWLEDGMENT

Halothane (Fluothane®) and propranolol (Inderal®) were contributed by Ayerst Laboratories.

REFERENCES

1. Wolfson S, Garlin R: Cardiovascular pharmacology of propranolol in man. Circulation 40:501-511, 1969

2. Prichard BNC, Gillam PMS: Assessment of propranolol in angina pectoris. Br Heart J 33:473-480, 1971

3. Prichard BNC, Gillam PMS: The treatment of hypertension with propranolol. Br Med J 1:7-16, 1969

4. Murmann W, Almirante L, Saccani-Guelfi M: Central nervous system of four β-adrenergic receptor blocking agents. J Pharm Pharmacol 18: 317-318, 1966

5. Bainbridge JG, Greenwood DT: Tranquillizing effects of propranolol demonstrated in rats. Neuropharmacology 10:453-458, 1971

6. Granville-Grossman KL, Turner P: The effect of propranolol on anxiety. Lancet 1:788-790, 1966

7. Waal HJ: Propranolol-induced depression. Br Med J 2:50, 1967

8. Fitzgerald JO: Perspectives in beta adrenergic blockade. Clin Pharmacol 10:292-306, 1969

9. Merin RG: Anesthetic management problems posed by therapeutic advances: III. Beta-adrenergic blocking drugs. Anesth & Analg 51:617-624, 1972

10. Merin RG, Tonnesen AL: Effect of beta adrenergic blockade on myocardial haemcdynamics and metabolism during light halothane anaesthesia. Can Anaesth Soc J 16:336-343, 1969

11. Jorfeldt L, Lofstrom B, Moller J, et al: Cardiovascular effects of beta-receptor blocking drugs during halothane anaesthesia in man. Acta Anaesthesiol Scand 14:35-44, 1970

12. Price HL, Skovsted P, Pauca AL, et al: Evidence for beta-receptor activation produced by halothane in normal man. Anesthesiology 32:389-395, 1970

13. Viljoen JF, Estafanous G, Kellner GA: Propranolol and cardiac surgery. J Thorac Cardiovasc Surg 64:826-830, 1972

14. Eger EI II, Saidman LJ, Brandstater B: Minimum alveolar anesthetic concentration: a standard of anesthetic potency. Anesthesiology 26:756-763, 1965

15. Eisele JH, Eger EI II, Muallem M: Narcotic properties of carbon dioxide in the dog. Anesthesiology 28:856-865, 1967

16. Regan MJ, Eger EI II: Effect of hypothermia in dogs on anesthetizing and apneic doses of inhalation agents. Anesthesiology 28:689-699, 1967

17. Leszkovsky G, Tardos LJ: Some effects of propranolol on the central nervous system. J Pharm Pharmacol 17:518-519, 1965

18. Murman W, Almirante L, Saccani-Guelfi M: Effects of hexobarbitone, ether, morphine and urethane upon the acute toxicity of propranolol and D-(−)-INPEA. J Pharm Pharmacol 18:692-694, 1966

19. Lader MH, Tyrer PJ: Central and peripheral effects of propranolol and sotalol in normal human subjects. Br J Pharmacol 45:557-560, 1972

20. Hayes A, Cooper RG: Studies on the absorption, distribution and excretion of propranolol in rat, dog and monkey. J Pharmacol Exp Ther 17: 302-311, 1971

21. Leonard BE: The effect of some β-adrenergic receptor blocking drugs on carbohydrate metabolism in mouse brain. Neuropharmacology 10:127-144, 1971

22. Grassi AO, de Lew MNF, Cingolani HE: Antilipolytic effect of propranolol in the dog. Life Sci 8:1239-1245, 1969

23. Esther C-J, Ammon HPT: The influence of the β-sympathicolytic agent propranolol on glycogenolysis and glycolysis in muscle, brain and liver of white mice. Biochem Pharmacol 15:2031-2035, 1966

24. Laverty R, Taylor KM: Propranolol uptake into the central nervous system and the effect on rat behavior and amine metabolism. J Pharm Pharmacol 20:605-609, 1968

25. Miller RD, Way WL, Eger EI II: The effects of alpha-methyl dopa, reserpine, guanethidine and iproniazid on minimum alveolar anesthetic requirement (MAC). Anesthesiology 29:1153-1158, 1968

STEROIDS AND HEPATITIS. Corticosteroids are the most widely used drug in severe viral hepatitis despite the lack of proven efficacy. In this study 29 patients with severe acute viral hepatitis were randomly assigned to a placebo or a methylprednisolone group for a 16 week treatment period. Both groups were comparable in clinical findings, laboratory results and presence of bridging necroses on liver biopsy. Seven of 14 patients receiving methylprednisolone (initially 48 mg gradually tapered to 12-32 mg during the last six weeks of treatment) and 2 of 15 receiving placebo died. Although these mortality differences were not statistically significant between groups a deleterious effect of steroids is suggested by the increased mortality in patients treated with methylprednisolone. Furthermore as many as 4 patients developed serious complications of steroid therapy during the study. In contrast, steroids are of proved efficacy in the treatment of chronic active hepatitis which is often associated with elevated immunoglobulins and autoimmune antibodies. The authors conclude that methylprednisolone did not improve the prognosis of severe acute viral hepatitis and may have produced a detrimental effect. *(Gregory PB, Knauer CM, Kempson RL et al: Steroid therapy in severe viral hepatitis. A double-blind, randomized trial of methylprednisolone versus placebo. NEJM 294:681-687, 1976)*

Circulatory Responses and Halothane Concentrations During Gastric or Gallbladder Traction With and Without Neuromuscular Blockade

ROBERT K. STOELTING, MD*
CHRISTINE PETERSON, RN†
JAMES A. MADURA, MD‡
Indianapolis, Indiana§

Systolic and diastolic blood pressures and heart rates did not change significantly and ventricular dysrhythmias did not occur during gastric or gallbladder traction in patients anesthetized with N_2O-halothane, with or without d-tubocurarine or pancuronium neuromuscular blockade.

Systolic and diastolic blood pressures and heart rates just before abdominal viscera traction were less ($p<0.05$) in patients paralyzed with d-tubocurarine than with pancuronium despite similar arterial halothane concentrations. In contrast, these measurements in patients without neuromuscular blockade were similar to those during pancuronium paralysis despite significantly greater arterial halothane concentrations in the unparalyzed patients.

The authors conclude that circulatory responses during gastric or gallbladder traction are clinically insignificant during N_2O-halothane administration, with or without d-tubocurarine or pancuronium neuromuscular blockade. Intraoperative blood pressures and heart rates were influenced by the neuromuscular blocker chosen. Neuromuscular blockade permitted anesthetic maintenance with lower arterial halothane concentrations than when paralysis was not present.

SUDDEN blood pressure decreases coincident with intra-abdominal operative manipulations may represent autonomic nervous system reflex responses.[1] Presumably, splanchnic sympathetic afferent fibers are stimulated and subsequent efferent activity produces splanchnic vasodilation with associated circulatory changes.[2] Burstein[1] described a celiac plexus reflex characterized by decreased systolic blood pressure, narrowed pulse pressure, and unchanged heart rate as most likely to occur during gallbladder or gastric operations. Circulatory responses with abdominal viscera manipulation during N_2O-halothane anesthesia have not been measured. Further, a speculated protective effect against autonomic nervous system reflexes by d-tubocurarine-produced autonomic ganglion blockade has not been documented.[3]

This report demonstrates that circulatory changes in response to gastric and/or gallbladder traction are minimal during N_2O-halothane anesthesia with or without d-tubocurarine (dTc) or pancuronium neuromuscular blockade. However, the neuromuscular blocker choice did influence the intraoperative blood pressures and heart rates, while

*Associate Professor of Anesthesia/Pharmacology.
†Anesthesia Research Nurse.
‡Assistant Professor of Surgery.
§Indiana University School of Medicine, Indianapolis, Indiana 46202.

Paper received: 12/9/74
Accepted for publication: 8/4/75

lower maintenance arterial halothane concentrations were present in paralyzed than in nonparalyzed patients.

METHODS

Twenty-seven chronically obese adults undergoing elective jejunoileal small bowel bypass operations were studied. All received morphine (6 to 10 mg) and scopolamine (0.4 to 0.6 mg) for preanesthetic medication. Anesthetic induction was with thiamylal (300 to 500 mg) and succinylcholine to facilitate endotracheal intubation. Ventilation was controlled with a volume ventilator adjusted to maintain $Paco_2$ near 30 torr. Anesthetic maintenance was with 60% N_2O-O_2 and halothane. Halothane was delivered from a Copper Kettle® vaporizer using systolic blood pressure as a guide for adjusting the vaporizer O_2 flow. Five minutes before the anticipated skin incision, 10 patients received 0.4 mg/kg of dTc and 10 patients received pancuronium (0.08 mg/kg). The remaining 7 patients received no neuromuscular blockers other than succinylcholine to facilitate intubation. Blood pressure was recorded continuously from an intra-arterial catheter placed in the radial artery. Heart rate and cardiac rhythm were determined from lead 2 of the ECG.

After the peritoneum was opened and before placement of any retractors, a control blood pressure and ECG were recorded and arterial blood was obtained for Pao_2, $Paco_2$, pH, and halothane concentration. Vaporizer O_2 flow and diluent gas flows had been unchanged for at least 10 minutes. Halothane concentrations were converted to equivalent MAC values, assuming a halothane blood-gas partition coefficient of 2.4 and a halothane MAC for this age group equal to 0.76 vol/100 ml.[4] Gastric traction was then applied for 30 seconds with blood pressure and ECG recorded continuously during and for 30 seconds after releasing the traction. When blood pressure and heart rate were again judged to be unchanging (3 to 5 minutes later) the same sequence was repeated with 30 seconds of gallbladder traction in only the paralyzed patients. Skeletal muscle relaxation was inadequate to permit gallbladder traction in the patients without neuromuscular blockade. Chronically obese patients undergoing similar operations were chosen to permit the same surgeon to provide the viscera traction in all patients.

Data were analyzed by Student's *t*-test and $p<0.05$ considered statistically significant. This study was approved by the Indiana University School of Medicine Clinical Research Committee.

RESULTS

All patient groups were similar with respect to age, weight, and preoperative blood pressure and heart rate (table 1). Control blood gases and pH were similar just before gastric traction, but arterial halothane concentrations were significantly less in the paralyzed patients. Control circulatory measurements (systolic and diastolic blood pressure and heart rate) during anesthesia and just before gastric traction were significantly less in patients paralyzed with dTc than in patients not paralyzed or those paralyzed with pancuronium (table 2).

Gastric traction did not significantly alter systolic and diastolic blood pressures or heart rates with or without competitive neuromuscular blockade (table 2). Likewise, gallbladder traction did not produce significant circulatory responses in paralyzed patients. No patient developed ventricular dysrhythmias.

The initial gastric traction was applied 39 ± 4 minutes (mean ± SE) after dTc administration and 40 ± 3 minutes following pancuronium. Twitch response to ulnar nerve stimulation (Peripheral Nerve Stimulator) was completely abolished in these patients. Ulnar nerve stimulation showed no evidence of neuromuscular blockade just before applying gastric traction in those patients receiving only succinylcholine for intubation.

DISCUSSION

Blood pressure and heart rate did not change significantly and ventricular dysrhythmias did not occur in response to gastric or gallbladder traction during N_2O-halothane anesthesia. Speculation that autonomic ganglion blockade from dTc might attenuate circulatory responses to intra-abdominal manipulation could not be confirmed, since significant changes did not occur with or without neuromuscular blockade.

Our findings are in contrast to those reported by Rocco and Vandam[5] describing arterial hypotension with or without bradycardia in 55/68 patients in response to manipulation of the abdominal viscera. However, these authors reported that circulatory changes occurred most often with stimulation of the parietal peritoneum, while gastric or gallbladder traction, as in our study,

TABLE 1

Comparative Patient Data (Mean ± SE)

	No neuromuscular blockade (n = 7)	d-Tubocurarine (n = 10)	Pancuronium (n = 10)
Preoperative			
Age	41 ± 3	38 ± 3	37 ± 2
Weight, kg	137 ± 10	133 ± 14	118 ± 11
Systolic blood pressure, torr	145 ± 9	133 ± 4	135 ± 4
Diastolic blood pressure, torr	90 ± 5	83 ± 2	82 ± 4
Heart rate, bpm	85 ± 4	91 ± 3	86 ± 2
Dose of competitive neuromuscular blocker administered, mg	None	53 ± 5	9.4 ± 2
Control measurements just before gastric traction			
Pa_{O_2} (F_{IO_2} = 0.4), torr	109 ± 15	103 ± 8	120 ± 12
Pa_{CO_2}, torr	32 ± 4	35 ± 2	33 ± 2
pH	7.42 ± 0.02	7.44 ± 0.02	7.49 ± 0.02
Arterial halothane, mg/100 ml	9.0 ± 0.5	4.1 ± 0.4*	5.0 ± 0.4*
Equivalent halothane MAC	0.62	0.28	0.34

n = number of patients.

*$p<0.05$ as compared with no neuromuscular blockade.

TABLE 2

Circulatory Responses to Gastric Tension (Mean ± SE)

	Immediately before gastric traction	30 seconds gastric traction	30 seconds after release gastric traction
Systolic blood pressure, torr			
No neuromuscular blockade	155 ± 7	147 ± 5	158 ± 8
d-Tubocurarine	119 ± 8*	108 ± 7	116 ± 9
Pancuronium	146 ± 9	135 ± 9	140 ± 7
Diastolic blood pressure, torr			
No neuromuscular blockade	102 ± 6	94 ± 7	105 ± 7
d-Tubocurarine	79 ± 5*	70 ± 5	76 ± 7
Pancuronium	88 ± 5	80 ± 6	85 ± 5
Heart rate, bpm			
No neuromuscular blockade	76 ± 5	77 ± 5	81 ± 7
d-Tubocurarine	61 ± 5*	59 ± 5	66 ± 5
Pancuronium	78 ± 5	75 ± 6	82 ±5

*$p<0.05$ compared with measurement in patients without neuromuscular blockade.

frequently produced no circulatory changes. Nevertheless, Smith[6] reported 10 instances of celiac plexus reflex responses, occasionally accompanied by an unobtainable blood pressure, during gastric or gallbladder traction.

Anesthetic agents may influence autonomic nervous system reflex activity. For example, Briscoe and Millar[7] reported that cyclopropane, diethyl ether, and halothane impaired sympathetic ganglion transmission. However, the role anesthetic agents may

have exerted on circulatory responses to abdominal viscera manipulation in our study or in previous reports[5,6] cannot be determined.

Despite similar arterial halothane concentrations, control systolic and diastolic blood pressures and heart rates were significantly less in patients paralyzed with dTc than in patients paralyzed with pancuronium. In addition, a significantly greater maintenance arterial halothane concentration was necessary to prevent movement during operation in unparalyzed patients. For example, greater than 1 MAC (about 0.5 MAC N_2O plus 0.62 MAC halothane) was present in unparalyzed patients, while less than 1 MAC (from the combined effects of N_2O plus halothane) was present in paralyzed patients. Even with the higher halothane concentrations, the intraoperative blood pressures tended to be greater than awake values in unparalyzed patients.

It is tempting to speculate that surgical stimulation was responsible, but it must be remembered that stimulation was similar in patients paralyzed with dTc and at lower halothane concentrations. Further, blood pressure measurements during pancuronium paralysis were also near the awake levels, but the arterial halothane concentrations were significantly less than in unparalyzed patients, being near those concentrations present during dTc paralysis. We conclude that this is evidence that the choice of neuromuscular blocker, as previously suggested,[8] may influence cardiovascular status during operation. Further, neuromuscular blockade permits maintenance of anesthesia with lower arterial halothane concentrations than when paralysis is not present.

Whether similar circulatory differences between dTc and pancuronium would be present with smaller doses of these drugs or lesser degrees of neuromuscular blockade cannot be stated. All our patients were obese, and calculation of neuromuscular blocker dose on the basis of body weight (mg/kg) resulted in large single-dose administration of dTc (average 53 mg) or pancuronium (average 9.4 mg). This produced a neuromuscular blockade characterized by no visible twitch response to ulnar nerve stimulation about 40 minutes later when the anesthetic concentration and circulatory measurements were determined.

If lower blood pressure during dTc paralysis reflects autonomic ganglion blockade, it is conceivable that smaller dTc doses would have produced less ganglion blockade and subsequent blood pressure decrease. As pancuronium produces little autonomic ganglion blockade, this should not be a consideration with the doses used in this study.[9]

REFERENCES

1. Burstein CL: Fundamental Considerations in Anesthesia. Second edition. New York, The Macmillan Company, 1955, pp 71-83

2. Cooperman LH: Effects of anaesthetics on the splanchnic circulation. Br J Anaesth 44:967-970, 1972

3. Burstein CL: Reflexes and curariform drugs (Questions and Answers). Anesth & Analg 41:79-80, 1962

4. Saidman LJ, Eger EI II, Munson ES, et al: Minimum alveolar concentrations of methoxyflurane, halothane, ether and cyclopropane in man: correlation with theories of anesthesia. Anesthesiology 28:994-1002, 1967

5. Rocco AG, Vandam LD: Changes in circulation consequent to manipulation during abdominal surgery. JAMA 164:14-18, 1957

6. Smith BH: Nature and treatment of coelic-plexus reflex in man. Lancet 2:223-227, 1953

7. Briscoe TJ, Millar RA: The effect of cyclopropane, halothane and ether on sympathetic ganglionic transmission. Br J Anaesth 38:3-12, 1966

8. Churchill-Davidson HC: A philosophy of relaxation. Anesth & Analg 52:495-501, 1973

9. Buckett WR, Marjoribanks CEB, Marwick FA, et al: The pharmacology of pancuronium bromide (ORG NA 97), a new potent steroidal neuromuscular blocking agent. Br J Pharmacol 32:671-682, 1968

Laryngotracheal Residue During Endotracheal Anesthesia

CHONG M. LEE, MD*
JAMES E. GILDEA, MD†
Hershey, Pennsylvania‡

THAT liquid residue may accumulate in the space between the cuff of the endotracheal tube and the larynx during general anesthesia has long been recognized in practice. A question arises, however, as to the amount of this matter that may remain in the trachea before extubation at the end of a surgical procedure. The present study was conducted to investigate, by the process of laryngotracheal toilet, the amount of such matter found in various clinical situations.

MATERIALS AND METHODS

Subjects were 83 unselected patients undergoing anesthesia for elective surgery. All were between 17 and 25 years of age and in ASA physical status I, II, or III. Patients were divided into 3 groups according to the operative position in which they were placed. All patients received IM 0.5 mg of atropine sulfate in conjunction with a sedative or narcotic 1 hour before operation. Sodium thiopental and succinylcholine were used to facilitate induction and intubation. Anesthesia was maintained with either N_2O, Innovar®, and muscle relaxant or enflurane and N_2O, with or without muscle relaxant. Respiration was assisted or controlled throughout.

The specially designed endotracheal tube (figure) was tested in 20 patients. After the tip of the endotracheal tube was passed beyond the vocal cord under direct laryngoscopy and the fluted proximal cuff was inflated, the tube was advanced until the distal margin of the inflated fluted cuff sat on the larynx tightly. Then the distal cuff was inflated and the tube was secured. Finally, the fluted cuff was deflated completely and the inflating tube was clamped to prevent self-inflation of the fluted cuff.

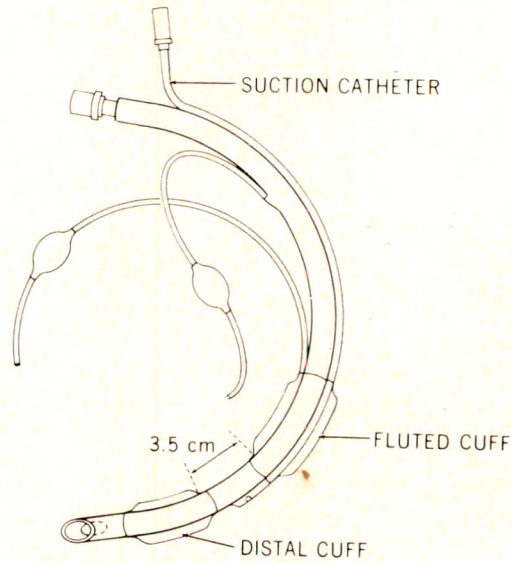


FIGURE. Combined 8 Portex endotracheal tube and suction catheter (12 French). Fluted cuff is inserted over endotracheal tube.

After the tube had been secured following intubation, an average of 2.4 ± 0.2 ml of normal saline solution was injected through the aspiration device on the endotracheal tube into the laryngotracheal space. The normal saline injected was aspirated immediately, and the volume recovered by this maneuver was measured. At the end of the

*Assistant Professor.
†Associate Professor.
‡Department of Anesthesia, Milton S. Hershey Medical Center, Pennsylvania State University, Hershey, Pennsylvania 17033.

Paper received: 6/5/75
Accepted for publication: 10/26/75

TABLE
Volume of Laryngotracheal Toilet During Endotracheal Anesthesia
(Mean ± SE)

		Number of patients	Volume, ml	p* values
Position	Supine[a]	31	1.3 ± 0.2	
	Trendelenburg[b]	32	0.2 ± 0.0	<0.001
	Sitting[c]	20	2.2 ± 0.3	<0.002
Sex	Male	40	1.6 ± 0.2	<0.001
	Female	43	0.7 ± 0.1	

*p: probability by t-test.

Average operation time: a - 152 ± 13 min
b - 125 ± 11 min
c - 183 ± 25 min

operation, the fluted proximal cuff was again inflated to obstruct the larynx from the oral cavity.

Laryngotracheal toilet was performed by means of suctioning the liquid matter into a Luken's tube and the volume measured. Student's t-test was used for statistical analysis of variance.

RESULTS

The specially designed endotracheal tube recovered 97.6% of the saline solution in the 20 patients tested with this device. No liquid residue was obtainable in 16 of the 32 patients in the Trendelenburg position, and less than 0.5 ml was recovered from each of the remainder of the patients in this group. The average volume (0.2 ± 0.0 ml) ($p<0.001$) in this group was significantly less than that of the supine group. An average of 1.3 ± 0.2 ml of laryngotracheal residue was aspirated from the supine patients. Those in sitting position had an average of 2.2 ± 0.3 ml, which was about 60% more than the supine group, a statistically significant difference ($p<0.02$) (table).

The additional variables studied showed that men patients (1.6 ± 0.2 ml) ($p<0.001$) demonstrated larger volumes than women (0.7 ± 0.1 ml). Neither duration of operation nor type of anesthetic showed statistically significant differences in volume.

DISCUSSION

The liquid matter found to accumulate in the space between the cuff of the endotracheal tube and the larynx during anesthesia with endotracheal tubes is probably a combination of laryngotracheal mucosa, saliva, regurgitated gastric contents, endotracheal tube lubricant, and blood from lacerated oropharyngeal mucosa. The differences in the amounts found in the 3 different positions studied may be primarily due to the gravity effect.

Metha[1] has suggested placement of the cuff just beyond the true vocal cord in order to eliminate this potential space in the trachea. He has also suggested tilting the operating table 10° head-down while suction is being applied through the endotracheal tube to perform laryngotracheal toilet.

Jamie[2] has also described a method of performing toilet: (1) To aspirate the liquid matter from the mouth and throat, close the expiratory valve of the anesthesia circuit, kink the cuff inflating tube, and remove the clamp. (2) Inflate the lungs by a hard squeeze on the reservoir bag; the cuff inflating tube is then released and the endotracheal tube is rapidly removed. The lungs deflate forcefully as the tube is removed and the liquid matter in the upper part of the trachea is expelled into the mouth.

Such an endotracheal tube with an airway aspiration device as described for the present study can be useful during routine endotracheal anesthesia for laryngotracheal toilet prior to extubation.

ACKNOWLEDGMENT

The authors thank Dr. Allen E. Yeakel for his help in the preparation of this manuscript.

REFERENCES

1. Metha S: The risk of aspiration in presence of cuffed endotracheal tubes. Br J Anaesth 44:601-605, 1972

2. Jamie AK: Laryngotracheal toilet before extubation. Anaesthesia 29:630-631, 1974

Butorphanol and Morphine: A Double-Blind Comparison of Their Parenteral Analgesic Activity

M. TAVAKOLI, MD*
G. CORSSEN, MD†
F. S. CARUSO, PhD‡

The analgesic effects of butorphanol tartrate and morphine sulfate were compared in 127 patients judged to have moderate to severe pain following major operations. The study was double-blind, and the drugs were given IM at several dosage levels. Scores for pain intensity and relief, as well as pain-intensity difference, were determind at 30, 60 and 120 minutes after medication, then were analyzed by a parallel-line assay method in a modified computer program. The analysis indicated butorphanol tartrate to be 7 times as potent as morphine sulfate. Peak analgesic effects were obtained at 60 minutes with both drugs. Side effects were minimal in degree and incidence. Neither butorphanol nor morphine induced any changes in blood pressure, pulse rate, or respiratory rate. These data, along with those from studies elsewhere, suggest that butorphanol is a safe, potent, and effective analgesic agent, with probably a low potential for inducing drug dependence.

OVER the years, a major objective of analgesic research has been to obtain an agent which retains the desirable analgesic property of morphine, has limited or no liability for producing physical dependence and can be totally synthesized without dependence on a supply of opium. Synthetic analgesics have been potent but they have also been highly addictive.

When it was observed that nalorphine, a narcotic antagonist, was also an effective analgetic,[1] a series of benzomorphans with concomitant analgesic and narcotic antagonist properties were synthesized.[2,3,4] The theoretical consideration that a molecule with both analgesic and narcotic antagonist properties would have a reduced liability for drug dependence proved correct, but psychotomimetic effects, occurring at or near therapeutically effective analgesic doses, added another dimension to the problem. In addition, usable agents were relatively weak analgesics compared to morphine.[5]

Recently, Monkovic's group[6,7] reported the total synthesis of butorphanol which is levo-N-cyclobutylmethyl-3,14-βdihydroxymorphinan (fig 1). Studies with this compound in laboratory animals demonstrated analgesic potency greater than morphine sulfate, narcotic antagonist activity equivalent to nalorphine,[8,9] a potent antitussive effect,[10] and an indication that its physical dependence liability was of a low level.[9,11] Data from studies conducted at the Addiction Research Center in Lexington, Kentucky, indicate a low physical dependence liability for butorphanol in human subjects.[12]

After butorphanol's safety and acceptability had been determined in normal volunteers and analgesic efficacy had been demonstrated in an open pain study, a comparison of butorphanol tartrate and morphine sulfate with respect to analgesic potency and incidence of side effects was undertaken as a double-blind study in postoperative

*Associate Professor, Department of Anesthesia, University of Alabama Medical Center, Birmingham, Alabama 35294.

†Professor and Chairman, Department of Anesthesia, University of Alabama Medical Center.

‡Medical Department, Bristol Laboratories, Syracuse, New York.

Paper received: 5/12/75
Accepted for publication: 9/1/75

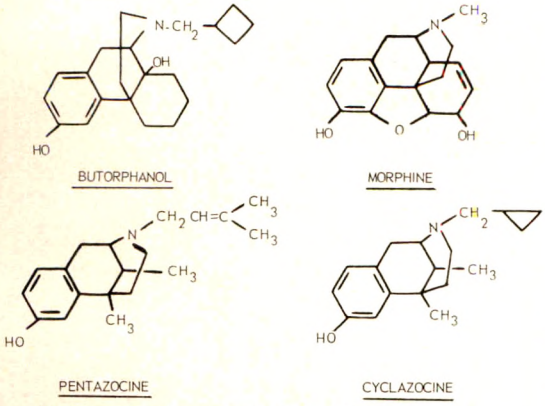


FIG 1. Structural formulas of butorphanol, morphine, pentazocine, and cyclazocine.

patients suffering moderate to severe pain. The results of this study are reported here.

METHODS AND MATERIALS

With an informed consent obtained in all instances, 127 patients meeting the investigative criteria were admitted to the study program. The men and women in the series were all adults judged able to evaluate and communicate their pain sensations. Pregnant individuals were not included, nor were patients with current or prior renal, hepatic, or hematologic disorders or a history of tolerance or addiction to narcotic drugs. Most of the patients had undergone major surgical procedures, including hysterectomy, laparotomy, hernia repair and arthroplasty.

The five groups were reasonably well balanced with respect to age, sex, weight, and intensity of initial pain (table 1). In all groups except that receiving the lowest dose of butorphanol, the distribution of female to male participants was about 2 to 1. The intensity of initial pain was predominantly rated severe in all groups.

Preoperative medication consisted of atropine or a combination of atropine and pentobarbital. Postoperatively, the experimental treatment consisted of single IM doses of either butorphanol tartrate at 0.73 mg (0.5 mg base), 1.46 mg (1 mg base), or 2.92 mg (2 mg base), or morphine sulfate at 5 mg or 10 mg. The test drugs were provided in identical vials* which were numbered consecutively and assigned to the patients in the order of their entrance into the study.

*Prepared and randomized as to drug and dose by Bristol Laboratories, Syracuse, New York.

Test agents were evaluated postsurgically in the recovery room. When the patient was alert enough to complain of pain, the degree was graded as 1=slight, 2=moderate, or 3=severe. Patients complaining of moderate or severe pain were assigned a patient number and then given an IM injection of 1 ml of the contents of the vial with the corresponding number.

After medication, close surveillance of the patient was maintained for a period of 5 hours. At 0.5, 1 and 2 hours following medication, the degree of pain was recorded and the degree of relief evaluated (0=no relief, 1=slight, 2=moderate, 3=good, and 4=complete). The difference between group mean scores initially and at each point of evaluation provided an additional index to drug effectiveness and was designated the pain intensity difference (PID). Blood pressure, pulse rate, and respiratory rate were determined each time the pain was evaluated. During the 5-hour period, it was left to the discretion of the investigator whether additional pain medication would be given at the patient's request.

On completion of the study, all the information was tabulated, the medication was decoded, and the data were analyzed. Summed values examined included (1) pain scores, (2) pain relief scores, (3) pain intensity differences. These were analyzed by a modified computer program for the parallel-line assay method as described by Finney[13] and others.[14] Analysis included (1) variance, (2) linear dose-response regressions, and (3) an estimate of butorphanol tartrate potency in relation to that of morphine sulfate.

RESULTS

Nine patients received additional medication during the primary 2-hour observation period; for purposes of statistical analysis, these patients were assigned pain intensity and relief scores of 3 (severe) and 0 (none), respectively. Omitted from statistical analysis was one patient (No. 31), receiving 2.92 mg of butorphanol, who, because of sleepiness and difficulty in breathing, was given 0.2 mg of naloxone intravenously 20 minutes after the initial medication. Also excluded from the analysis were patients No. 38, 91 and 101, who did not receive medication because these test vials had either been broken or inadvertently discarded.

The mean values for blood pressure, pulse, and respiratory rate recorded during

TABLE 1

Drug Groups: Randomization Schedule and Vital Statistics

	Randomization schedule	Age	Weight	Sex	Race	Initial pain intensity	Remedication requested
Butorphanol tartrate 0.73 mg salt (0.5 mg base)	1,7,16,18,21,22,35,37,43,47[a],54,58,64,69, 76[a],77,82,87[a],92,98,102,104,115,117, 124[a],127	Low: 20 High: 58 Median: 35	110 220 153	M: 11 F: 15 N= 26	W: 13 B: 13	M(2): 5 S(3): 21	None: 5 <2 hr: 11 2-3 hr: 6 3-4 hr: 2 >4 hr: 2
2.92 mg salt (2 mg base)	2,4,11,15,23,26,32,33,42,49,55,56,65,67, 72,78,81,84,99,100,108,110,114,116, 121,125	Low: 21 High: 68 Median: 33	100 280 156.5	M: 8 F: 18 N= 26	W: 11 B: 15	M(2): 4 S(3): 22	None: 10 <2 hr: 4 2-3 hr: 6 3-4 hr: 4 >4 hr: 2
2.92 mg salt (2 mg base)	3,8,19,20,27[a],28,31[b],36,45,48,51,53,66, 68,71,73,83,85,94,95,103,113,118,122, 123,101[c]	Low: 18 High: 62 Median: 27	98 200 131	M: 7 F: 18 N= 25	W: 17 B: 8	M(2): 4 S(3): 21	None: 8 <2 hr: 3 2-3 hr: 6 3-4 hr: 3 >4 hr: 4
Morphine sulfate 5 mg salt	9,10,13,14,24[a],29,38[c],39,41,50,59,60[a], 62,63,74[a],75,86,88,96,97,106,109,119, 120,126,128	Low: 18 High: 52 Median: 31	107 229 151	M: 7 F: 18 N= 25	W: 16 B: 9	M(2): 8 S(3): 17	None: 7 <2 hr: 10 2-3 hr: 3 3-4 hr: 4 >4 hr: 1
10 mg salt	5,6,12,17,25,30,34,40,44,46,52,57,61,70, 79,80[a],89,90,93,105,107,91[c],111,112, 129,103	Low: 21 High: 67 Median: 36	94 232 162	M: 8 F: 17 N= 25	W: 16 B: 9	M(2): 6 S(3): 19	None: 11 <2 hr: 7 2-3 hr: 1 3-4 hr: 1 >5 hr: 5

a. Remedication prior to 2 hr.

b. Excluded from analysis—received naloxone.

c. Vials accidentally broken or discarded (pt 38,91,101).

the two-hour period following medication showed no statistically significant changes within or between any of the 5 treatment groups. The means and standard errors of the various scores related to pain are listed in table 2 and graphically presented in figures 2, 3 and 4.

The response obtained with the 0.73 mg dose of butorphanol tartrate was significantly less than the responses to the two higher doses, 1.46 and 2.92 mg, but the latter doses did not significantly differ from each other. Also, the low dose of morphine sulfate was significantly less effective than the high dose. Thus, the sensitivity of this method for determining analgesic activity and differentiating between doses was evident.

With respect to relative potency, there was no statistical difference between 0.73 mg butorphanol tartrate and 5 mg morphine sulfate, or between 1.46 or 2.92 mg butorphanol tartrate and 10 mg morphine sulfate.

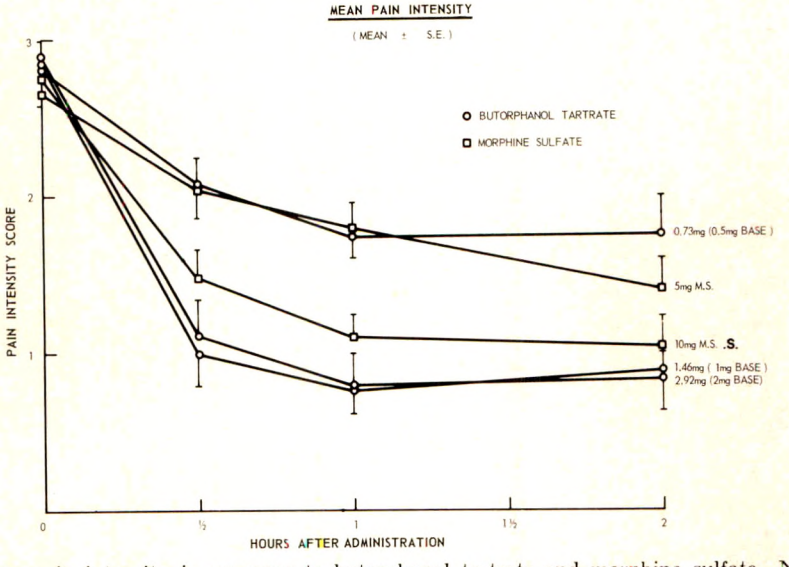


FIG 2. Mean pain intensity in response to butorphanol tartrate and morphine sulfate. Note that 0.73 mg butorphanol tartrate appears equivalent to 5 mg morphine sulfate and that 1.45 mg and 2.92 mg butorphanol tartrate appear slightly greater than 10 mg morphine sulfate. These data support the conclusion that butorphanol tartrate is 7 times as potent as morphine sulfate.

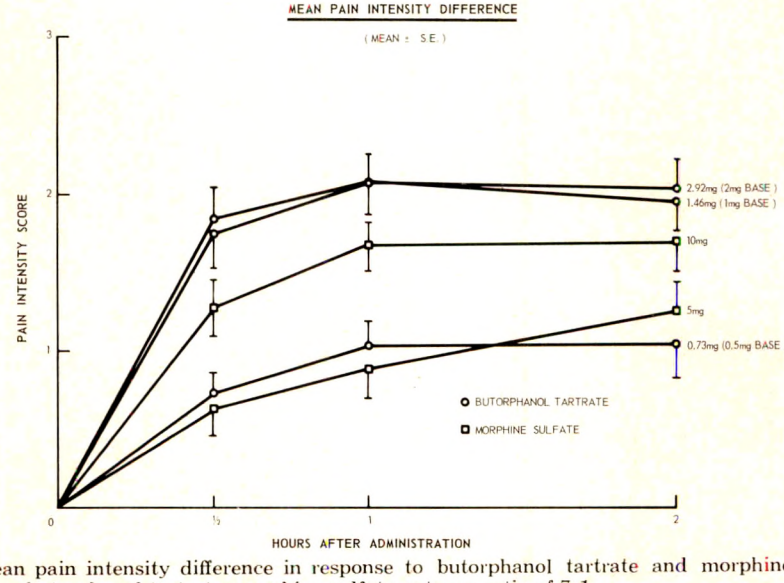


FIG 3. Mean pain intensity difference in response to butorphanol tartrate and morphine sulfate. The data indicate a butorphanol tartrate:morphine sulfate potency ratio of 7:1.

TABLE 2

Summary of the Scores Obtained for the Various Parameters Employed in Assessing Analgesic Activity (Mean ± SE)

		Butorphanol tartrate as salt (base equivalent)						Morphine sulfate		
	Hours	N	0.73 mg (0.5)	N	1.46 mg (1)	N	2.92 mg (2)	N	5 mg	N	10mg
Pain intensity	0	26	2.81 ± 0.08	26	2.85 ± 0.07	24	2.88 ± 0.07	25	2.68 ± 0.10	25	2.76 ± 0.09
	½	26	2.08 ± 0.17	26	1.00 ± 0.20	24	1.12 ± 0.21*†	25	2.04 ± 0.18	25	1.48 ± 0.17‡§
	1	26	1.77 ± 0.17	26	0.77 ± 0.16	24	0.79 ± 0.20*†	25	1.80 ± 0.16	25	1.08 ± 0.17§
	2	22	1.77 ± 0.22	26	0.88 ± 0.17	23	0.83 ± 0.20*†	22	1.41 ± 0.18	24	1.04 ± 0.19‡§
Total		22	8.05 ± 0.50	26	5.50 ± 0.50	23	5.43 ± 0.53*†	22	7.77 ± 0.52	24	6.25 ± 0.51‡§
Pain intensity difference (PID)	½	26	0.73 ± 0.15	26	1.85 ± 0.20	24	1.75 ± 0.21*†	25	0.64 ± 0.16	25	1.28 ± 0.18‡§
	1	26	1.04 ± 0.16	26	2.08 ± 0.17	24	2.08 ± 0.20*†	25	0.88 ± 0.17	25	1.68 ± 0.16§
	2	22	1.05 ± 0.21	26	1.96 ± 0.17	23	2.04 ± 0.19*†	22	1.27 ± 0.19	24	1.71 ± 0.20‡§
Total		22	3.09 ± 0.46	26	5.88 ± 0.50	23	6.04 ± 0.52*†	22	2.95 ± 0.49	24	4.75 ± 0.49‡§
Pain relief	½	26	1.08 ± 0.24	26	2.62 ± 0.29	24	2.58 ± 0.29*†	25	0.96 ± 0.24	25	1.84 ± 0.29†§
	1	26	1.46 ± 0.24	26	2.92 ± 0.24	24	2.96 ± 0.28*†	25	1.28 ± 0.24	25	2.52 ± 0.25§
	2	22	1.55 ± 0.30	26	2.77 ± 0.25	23	2.91 ± 0.27*†	22	1.82 ± 0.28	24	2.50 ± 0.28‡§
Total		22	4.50 ± 0.69	26	8.31 ± 0.71	23	8.70 ± 0.73*†	22	4.18 ± 0.73	24	6.96 ± 0.76‡§

*Butorphanol; 2.92 mg statistically different from 0.73 mg at 0.01 level.

†Butorphanol tartrate, 2.92 mg, statistically different from morphine sulfate, 5 mg (2 hr at 0.05 level); ½, 1 hr and total at 0.01 level).

‡Morphine sulfate; 10 mg statistically different from 5 mg (½ hr and total at 0.05 level; 2 hr at 0.01 level).

§Morphine sulfate, 10 mg, statistically different from butorphanol tartrate, 0.73 mg (½, 2 hr, and total at 0.05 level; 1 hr at 0.01 level).

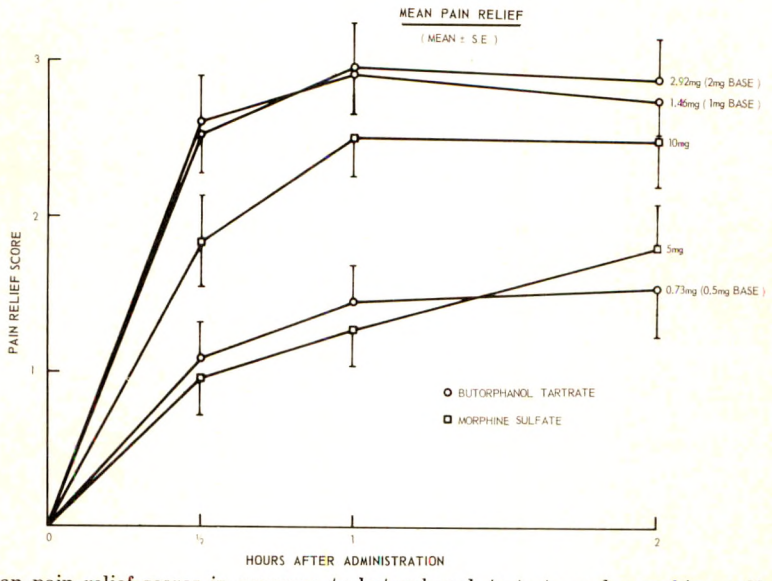


FIG 4. Mean pain relief scores in response to butorphanol tartrate and morphine sulfate. These data provide further support for a 7:1 butorphanol tartrate:morphine sulfate potency ratio.

When the parallel-line assay method was applied to the sums of pain intensity, pain-intensity difference, and pain relief, sufficient linearity and parallelism were obtained to validate the use of this method. The sum of pain intensity proved to be the most reliable for estimating relative milligram:milligram potency of the two agents. Calculations indicated that butorphanol tartrate was seven times as potent as morphine sulfate as an analgesic agent.

The incidence and type of side effects were not remarkable (table 3). With butorphanol, the predominant side effect was drowsiness; there were two instances of nausea. Results with morphine sulfate were similar. The number of side effects reported was so minimal that statistical evaluation was not warranted.

DISCUSSION

The clinical measurement of pain and its relief constitutes a difficult area of research. Attempts at measurement are strongly influenced and complicated by personal and environmental factors as well as by extenuating physical or psychological circumstances. These variables make it difficult to obtain a study population sufficiently homogeneous for a comparative analgesic bioassay. In the study described above, the test groups were relatively homogeneous as indicated by the vital statistics (table 1) and the definite responses to medication. Statistically significant differences in effectiveness were established between the low and high doses for each of the test drugs.

However, variability associated with biological response and with uncontrollable

TABLE 3
Summary of Incidence and Type of Side Effects Reported

	Side effect	½ hr	1 hr	2 hr
Butorphanol tartrate 0.73 mg (0.5 mg base)	Sleepy	1	—	—
Butorphanol tartrate 1.46 mg (1 mg base)	Drowsiness/sleepiness,	1	4	1
	nausea	—	—	1
Butorphanol tartrate 2.92 mg (2 mg base)	Drowsiness/sleepiness,	3	4	2
	nausea	—	—	1
Morphine sulfate 5 mg	Drowsiness/sleepiness,	—	2	2
	nausea	—	—	1
Morphine sulfate 10 mg	Nausea	1	1	1
	Nausea and vomiting	—	—	1

factors within a test population always influences biologic assays. The fact that the two larger doses of butorphanol tartrate did not differ significantly from each other does not necessarily indicate a ceiling effect, but is more likely a reflection of biologic variability and the close interval between doses. In a similar study by Dobkin,[15] the same low and mid doses of butorphanol did not differ statistically over the entire two-hour observation period, but they were effective analgesic doses and the effects were distinquishable at the half-hour interval. A more recent study by the same investigators demonstrated dose-related responses at 1 mg, 2 mg and 4 mg of butorphanol tartrate, with the largest dose affording almost complete relief of pain.[16]

Data from our study suggest that in providing relief from pain (table 2 and fig 2-4), the low doses of butorphanol and morphine were approximately equivalent, and that either the mid or the high dose of butorphanol was approximately equivalent to the high dose of morphine sulfate. Because of the variables noted above, the latter relationship is open to question.

Dobkin[15] reported this same magnitude of potency difference as we found (7:1) between butorphanol tartrate and morphine sulfate. Possibly, when the dose intervals with butorphanol tartrate and the size of the test population are expanded, 1.46 mg will approximate 10 mg morphine sulfate, and larger doses of butorphanol will exceed this in effectiveness.

Following IM administration, all doses of butorphanol tartrate achieved maximal effects within one hour (fig 2-4), and in each instance this maximal level was maintained to two hours, the last observation period for which a score was determined. With morphine sulfate, the effect of the 5 mg dose seemed more pronounced at the latter point than 0.73 mg of butorphanol tartrate. Although duration of effect was not an objective of this study, the data suggest that butorphanol effects probably last about as long as those of morphine sulfate.

At the doses used, neither butorphanol nor morphine induced any changes in vital signs or any significant side effects (table 3). Although respiratory depression is known to be associated with morphine, no such effect was observed with either butorphanol or morphine in our study.

Since the respiratory effect of morphine and butorphanol was not the subject of this study, no blood gas determinations or pulmonary volume measurements were made. Only the respiratory rate was counted. However, our impression to date is that butorphanol tartrate will prove to have only a limited depressant effect on respiration. More significant is the observation that the definitely analgesic doses of butorphanol in this study gave no evidence of causing mental aberration.

Currently available information thus indicates that butorphanol tartrate is a safe, potent, and effective analgesic agent with minimal undesirable side effects. If the expectation of minimal liability for producing physical dependence is fulfilled, this drug should find an important place among the analgesic agents now in use.

REFERENCES

1. Lasagna L, Beecher HK: The analgesic effectiveness of nalorphine and nalorphine-morphine combinations in man. J Pharmacol Exp Ther 112: 356-363, 1954

2. Harris LS, Pierson AK: Some narcotic antagonists in the benzomorphan series. J Pharmacol Exp Ther 143:141-148, 1964

3. Gordon RA, Morgan JH: Studies of pentazocine (WIN 20,228). 1. Evaluation as an analgesic in post-operative patients. Can Anaesth Soc J 12: 331-336, 1965

4. Jasinski DR, Martin WR, Hoeldtke RD: Effect of short and long term administration of pentazocine in man. Clin Pharmacol Ther 11:385-403, 1970

5. Houde RW: Management of pain, Diagnosis and Management of Cancer. Edited by RL Clark, Chicago, Year Book Medical Publishers, 1971, vol III, Oncology, p 489

6. Monkovic I: Synthetic 14-hydroxymorphinan narcotic antagonists. Iowa City, Iowa, ACS Division of Medicinal Chemistry, Abstracts of 13th National Medicinal Chemistry Symposium, 1972

7. Monkovic I, Conway TT, Wang H, et al: Total synthesis and pharmacological activities of N-substituted 3,14-dihydroxymorphinans. J Am Chem Soc 95:7910-7912, 1973

8. Gordon M, Pircio AW, Caruso FS, et al: Approaches to the problem of opiate abuse. Report of the Committee on Problems of Drug Dependence, 1974

9. Pircio AW, Gylys JA, Cavanagh RL, et al: Pharmacology of butorphanol, a new potent antagonist analgetic agent. Arch Int Pharmacodyn Therap (in press)

10. Cavanagh RL, Gylys JA, Bierwagen ME: Antitussive properties of butorphanol. Arch Int Pharmacodyn Therap (in press)

11. Swain HH, Villarreal JE, Seevers MH: Evaluation of new compounds for morphine-like

physical dependence in the rhesus monkey. Report of the Committee on Problems of Drug Dependence, Addendum, 1973, pp 695-696

12. Jasinski DR, Griffith JD, Pevnick JS, et al: Progress Reports on Studies from the Clinical Pharmacology Section of the Addiction Research Center. Proceedings: Problems of Drug Dependence, pp 136-149, 1975

13. Finney DJ: Statistical Method in Biological Assay. Second edition. New York, Hafner Publishing Company, 1964

14. McArthur JW, Ulfelder H, Finney DJ: A flexible computer program for the composite analysis of symmetrical and asymmetrical biological assays of parallel-line type. J Pharmacol Exp Ther 153: 573-580, 1966

15. Dobkin AB, Eamkaow S, Zak S, et al: Butorphanol: a double-blind evaluation in post-operative patients with moderate or severe pain. Can Anaesth Soc J 21:600-610, 1974

16. Dobkin AB, Eamkaow S, Caruso FS: Double-blind comparison of butorphanol and pentazocine in patients with severe post-operative pain. Clin Pharmacol Ther Vol 18, No. 5, Part 1, pp 547-553, November, 1975

TRACHEAL TUBE POSITION. Movement of an endotracheal tube may occur with changes in head position. The authors investigated tube position in the trachea by radiographs taken in the semisitting position with the head flexed, extended or laterally rotated. Twenty adult patients intubated orally or nasally with an 8.0 mm endotracheal tube were studied. The tube moved a similar distance regardless of the route of intubation or status of cuff inflation. The distal end of the tube moved an average of 1.9 cm toward the carina with head flexion from a neutral position, 1.9 cm away from the carina with extension and 0.7 cm away with lateral head rotation. The carina was noted to move in the same direction as the tube thus minimizing the apparent tube to carina movement. These data suggest that inadverent extubation or endobronchial intubation could occur with the extremes of head movement from a neutral position. Head position should be considered when evaluating distal tube position in the trachea with chest radiographs. *(Conrardy PA, Goodman LR, Lainge F et al: Alteration of endotracheal tube position. Flexion and extension of the neck. Crit Care Med 4:8-12, 1976)*

Nitrous Oxide Encephalography: 5-Year Experience with 475 Pediatric Patients

RICHARD A. ELWYN, MD*
WALLACE H. RING, MD†
EDWARD LOESER, MD‡
GARTH G. MYERS, MD§
Salt Lake City, Utah‖

475 pediatric patients with a variety of neurologic conditions were subjected to encephalography, using N_2O as the contrast medium and N_2O-halothane as anesthetic agents. This technic is both safe and effective, as reflected by no mortality and satisfactory roentgenograms. By application of the principles of gas physics, postoperative discomfort has been greatly reduced, resulting in a more comfortable convalescence and earlier discharge.

A KNOWLEDGE of gas physics and pharmacokinetics is essential for safe anesthetic administration, and the dangers associated with the use of high concentrations of N_2O have received the attention of many authors. Saidman and Eger[1] warned that, during N_2O anesthesia, this gas may diffuse into entrapped air spaces and result in increased volume and/or pressure. They also suggested that use of N_2O as a contrast medium during pneumoencephalography (PEG) might prove advantageous to the patient, provided the same gas was used for general anesthesia. Munson[2] has warned that small air emboli may expand into larger bubbles during N_2O anesthesia.

By recognition of these characteristics of N_2O, we have attempted to provide patients undergoing gas PEG with a measure of operative safety, pain relief, and postoperative comfort not previously afforded with other modalities.

The technic described is unique in that a major reason for administering general anesthesia is not only to provide intraoperative pain relief, but to reduce postoperative discomfort.

METHOD

Observations were made on 538 pediatric patients subjected to PEG. Of these, the contrast medium was N_2O in 475 and air in 63. Patients with known increased intracranial pressure were examined by ventriculograms.

Infants up to 1 year of age received only atropine premedication, 0.02 mg/kg, just before the procedure. Older children received 2.2 to 4.4 mg/kg of hydroxyzine or 0.02 mg/kg of diazepam orally 4 hours preoperatively, followed by 2.2 to 6.6 mg/kg of pentobarbital or secobarbital 1 to 2 hours preoperatively and atropine. [We tended to omit the heavier premedication during the last 200 patients in the study, to have the children awake at the conclusion of the procedure.]

*Associate Clinical Professor.
†Assistant Clinical Professor.
‡Instructor.
§Director, Birth Defects Clinic, Primary Children's Medical Center.
‖Department of Anesthesiology, Primary Children's Medical Center, University of Utah, Salt Lake City, Utah 84103

Paper received: 6/4/75
Accepted for publication: 10/27/75

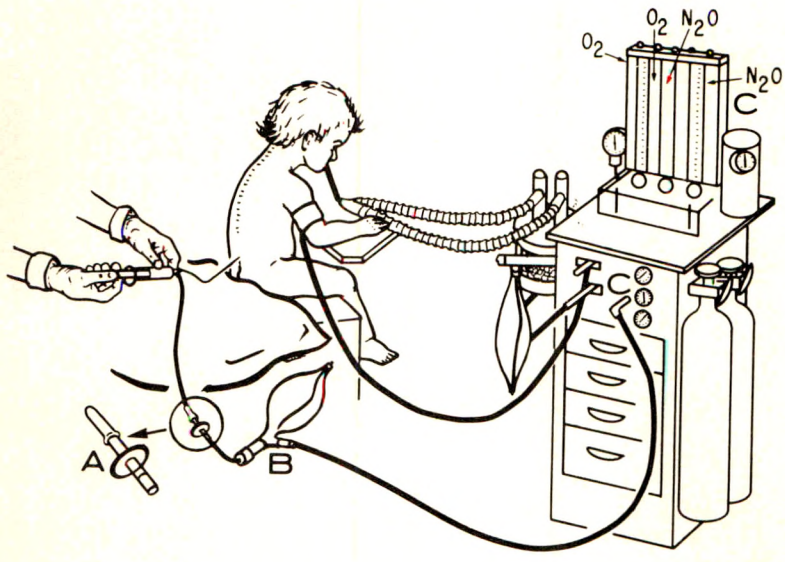


FIG 1. A. Sterile gas filter. B. Reservoir bag. C. Special N_2O flowmeter and outlet.

Anesthesia was induced with N_2O-O_2 (70:30) and 1% to 4% halothane in all patients and maintained by 0.25% to 1.0% halothane-N_2O-O_2 in N_2O-medium patients at the lightest level possible. In patients given air as the contrast medium, anesthesia was maintained with halothane and O_2, without N_2O. The vocal cords and trachea were sprayed with 4% lidocaine at a light level of anesthesia for endotracheal intubation. Respirations were controlled in most patients during the study period.

Blood pressure was monitored in all patients by the standard cuff technic and heart sounds by esophageal or precordial stethoscope. The legs were wrapped with elastic bandages prior to placement of the child in the sitting position.

Lumbar puncture and intrathecal gas instillation followed the usual sterile precautions. Opening pressures were determined at the level of the inion in the sitting position, usually 15 to 20 minutes after induction of anesthesia. The N_2O from a specially modified anesthesia machine (fig 1) was delivered into a reservoir bag, through a gas filter and into a sterile syringe. The cerebrospinal fluid (CSF) pressure was checked before withdrawal of the lumbar puncture needle, after the radiologist estimated that roentgenograms showed sufficient ventricular gas, and the total amount of gas injected and CSF removed was recorded. Patients were then placed supine and wrapped in a warming mattress maintained at 38° C. Nine radiographic films were taken by the usual PEG methods and body positions. In N_2O contrast medium patients the anesthetic administration was continued with 65% to 75% N_2O and halothane, until the attending physician determined that the roentgenograms were satisfactory. On completion of the examination, and after return to spontaneous ventilation, patients were extubated and taken to the recovery room. O_2 was given by face mask for the following hour.

Roentgenograms for gas persistence in the ventricles were taken on 10 randomly selected cases at 15 minutes, 1 hour, and 4 hours after anesthesia in N_2O-contrast patients.

Assessable patients 6 years old and over were evaluated for the presence and severity of headaches over a 5-day post-PEG period. Since the evaluation of headache is largely subjective by the observer as well as the patient, it was felt important that the study not influence the observer. All observations noted on the chart by the nurses were their own comments, as were their evaluations of the presence and severity of headaches. A headache was recorded as severe if the patient was essentially incapacitated, moderate if the child preferred to remain in bed except for toilet privileges, and mild if the child was up and about but complained of headache. Assessable patients were those

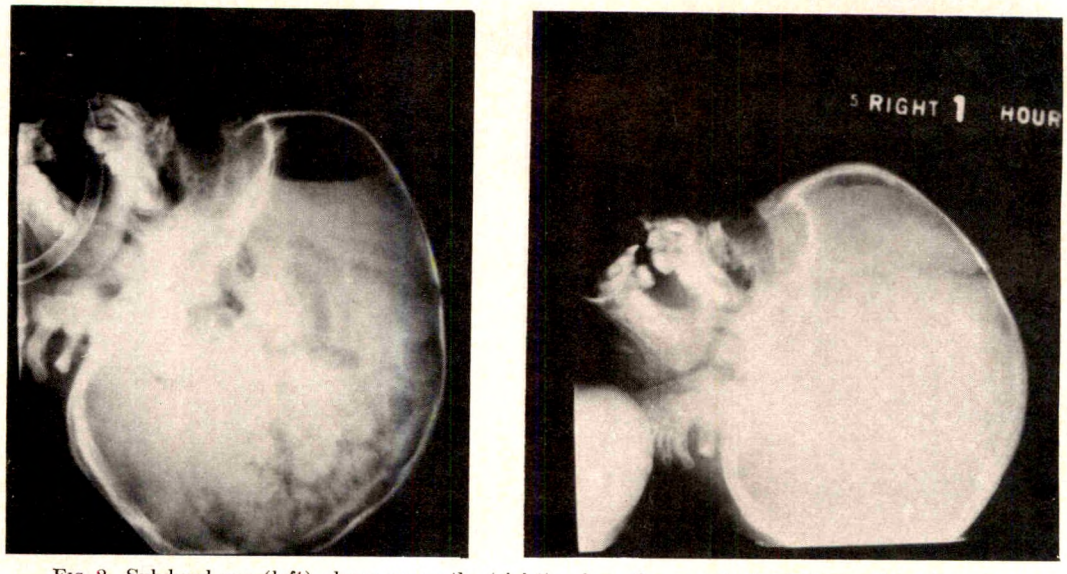


FIG 2. Subdural gas (left) clears promptly (right) when the anesthetic N_2O is discontinued.

not going to surgery or for other tests requiring sedation or anesthesia within the study period.

As hospital discharge is a definite endpoint, an analysis of the time from the PEG to hospital release was made in patients receiving no further procedures or tests. Anesthetic records and hospital charts were reviewed for neurologic and anesthetic complications. Emesis was tabulated from nursing notes.

RESULTS

The table summarizes headache incidence and duration in patients 6 years of age and older. There were no incapacitating or severe headaches in patients where N_2O was the contrast medium, while 44% of air-contrast patients had a severe headache at 1 day. The severe headaches with air-contrast studies lasted up to 4 days in 1 patient, but were usually decreasing at 2 days.

Although nearly half of the 437 patients vomited within the immediate postanesthetic period, all but 3% of the N_2O-contrast patients were no longer vomiting at 24 hours, and no N_2O-contrast patients vomited at 48 or 72 hours, while 5% of air patients still vomited at 72 hours.

Of 274 patients whose records were analyzed for time of hospital discharge, all the N_2O-contrast patients (n=255) went home by 96 hours while only 74% of 19 air-contrast patients were so fortunate. At 144 hours, 5% of the air-contrast group were still in the hospital.

Of the total 475 patients given N_2O, radiologic results were considered satisfactory by the pediatric roentgenologist in 93%, compared with 81% satisfactory results in the 63 air-contrast patients. In the N_2O group, 6.8% of the films were technically unsatisfactory, while 17.4% in the air-contrast group were so classified. An examination was listed as technically unsatisfactory if spinal tap did not produce CSF, the contrast gas did not reach the cerebral ventricles in quantity sufficient for good films, or excessive contrast gas in the subdural space obscured other structures. The only N_2O-contrast PEG with poor films resulted from operative depletion of an N_2O cylinder and subsequent loss of ventricular N_2O. Nitrous oxide injection ranged from 2-4 times the amount of CSF removed. The usual duration of anesthesia was 1½ hours.

TABLE

Incidence of Headache in 139 Children Undergoing N_2O Encephalography (Ages 6 Years and Over)

	Contrast gas			
	N_2O (n = 121)		Air (n = 18)	
Head-ache	Mild (percent)	Severe	Mild (percent)	Severe
Hours post-EEG				
24-36	25	0	45	44
48	9	0	22	39
72	1	0	33	11
96	0	0	16	6
120	0	0	11	0

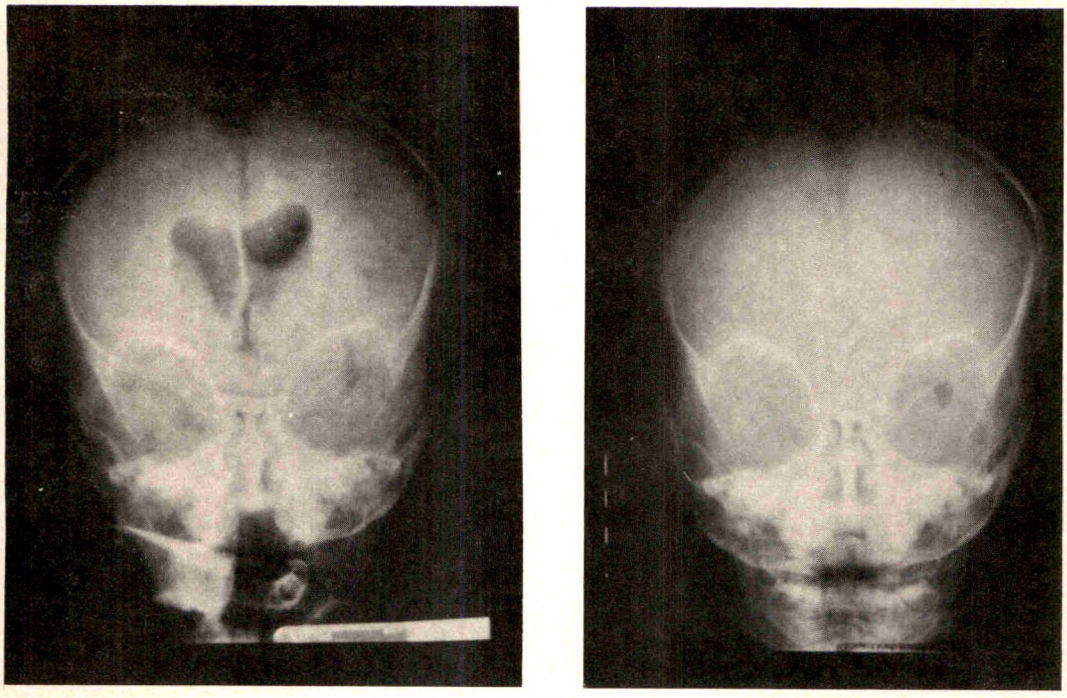


FIG 3. In the majority of cases x-rayed N_2O in the ventricles was almost completely gone by 15 min. postexamination.

X-rays on 10 patients taken for persistence of ventricular contrast gas revealed that only minimal gas remained at 15 minutes after cessation of the N_2O anesthetic (fig 3). Our N_2O medium infants showed minimal postoperative symptomatology but a temperature spike at 4 to 8 hours was not uncommon.

There were no fatalities in our series of 538 examinations and no neurologic complications. Operative complications included: (1) 6 cases of marked bradycardia, one of which resulted in a severe but rapidly reversible hypotension; (2) 3 patients (including the preceding) with severe hypotension, which occurred when the patient was placed in the sitting from the supine position; (3) 2 cardiac arrests, one following an inadvertent extubation and one in whom the exact cause was not identified but felt due to excessive anesthetic concentrations. (Both patients were resuscitated and recovered uneventfully.); (4) 8 extubations with reintubation accomplished without incident (except in [3] above).

Postoperatively, 18 patients developed croup.

DISCUSSION

The technic of using a gas to visualize the ventricular system has been used for over 57 years. The instillation of 20 ml of air causes an acute reaction in the awake patient; headache, pallor, sweating, bradycardia, hypotension, nausea and vomiting occur with varying severity. The examination requires pain obtundation, and the resulting depression can easily result in airway obstruction and hypoxia. In adults, local or sedation is usually satisfactory. Children, because of their temperment, require heavy sedation or general anesthesia. Well-managed general endotracheal anesthesia will eliminate airway obstruction and is recommended by textbooks of pediatric anesthesia.[3,4] In addition, while ketamine or neuroleptanesthesia may be effective operatively, they do not concern themselves with the *postoperative* morbidity. Our technique, with administration of general anesthesia, not only provides intraoperative pain relief but also reduces postoperative discomfort.

After the completion of air encephalography, most patients experience headache and nausea for a day or more, and air may remain in the ventricles for a week or longer. A temporary sterile meningitis develops, with a fever spike at 4 to 8 hours and an increase in protein and cell count lasting 2 to 3 days.

To find a better contrast gas medium than air, Aird[5] injected N_2O for dog encephalograms under local anesthesia, demonstrating its safety and showing total absorption within 1 hour. Newman,[6] also using local anesthesia, injected N_2O in humans undergoing encephalography but the N_2O diffused too rapidly from the ventricles for satisfactory roentgenograms. Since both Aird and Newman found cerebrospinal reactions with N_2O to be similar to those with air, we did not do routine postencephalogram lumbar punctures to establish the safety of N_2O by the lumbar route. We did, however, add the use of a bacterial filter to assure sterility in the examination.

We have carried Newman's study a step further by using N_2O for both general anesthesia and as the contrast medium. Since 100% N_2O is injected as the contrast gas and since only 65% to75% N_2O is administered in the anesthetic mixture, a pressure decrease would be expected after the injection because of the slightly greater partial pressure of N_2O in the ventricles than in the blood and brain. We found it necessary to inject 2 to 4 times as much N_2O as the contrast gas as would have been used with air as the contrast gas. In no case did the closing pressure reach a higher level than the opening pressure. As long as N_2O was continued in the anesthetic mixture in 65% or greater concentrations, sufficient gas remained in the ventricular system for satisfactory roentgenograms.

Smith and Crothers,[7] reviewing 80 PEG procedures in children <2 years of age, found subdural gas in 70%. Many of these infants had stormy postinjection courses, relieved promptly by puncture of the subdural space and gas withdrawal. With N_2O as the contrast gas, subdural gas may occur (fig 2, left) with the same frequency, but it is rapidly removed when the anesthetic N_2O is discontinued (fig 2, right). The result will be decreased CSF pressure within 15 minutes. The few postoperative symptoms reported in Results were presumably due to the irritative effects of N_2O and were related to the time of contact of the N_2O with the ventricular walls.

In the majority of cases, only minimal gas was seen on roentgenograms taken 15 minutes after N_2O cessation (fig 3). This small amount of gas remaining in the ventricles most likely represented inward diffusion of air or O_2 as the N_2O diffused out. The mask O_2 given patients should cause the more soluble O_2 to diffuse in first and later be replaced by N_2, each replacement lowering the amount of residual gas. Davidoff and Dyke[8] found that the duration of symptoms in days after gas PEG was in direct proportion to the amount of gas injected, relative to ventricular size. Schwab and von Storch[9] found that the severity of CSF cellular reaction varied directly with the volume of air used, and that the patients' symptoms were quantitatively related to the degree of cellular reaction. Davidoff[8] also recognized that the aim of the treatment in reducing morbidity from gas PEG should be to eliminate the gas as fast as possible after the examination. The rapid elimination of N_2O medium from the ventricles was most likely responsible for our decreased duration of postinjection symptomatology. Thus we agree with Davidoff that the duration of contact of the contrast gas with the ventricular system is responsible for most morbidity.

Davidoff, using air contrast in 94 patients, found 26% moderate or severe headaches at 48 hours and 5% remaining at 120 hours. Vomiting occurred in 8% of his patients at 48 hours, 7% at 72 hours, and 3% at 120 hours. We have listed his morbidity because of our paucity of air-contrast studies and to point out why hospital discharge time was shorter in our N_2O-contrast patients. Our N_2O medium patients were comfortable sooner despite the large volumes injected, up to 275 ml.

Mortality associated with gas encephalography has been reported as 0.2[8] to 8.2%.[10] Air embolism and brain herniation comprise the main reasons for death. Some of the unreported causes of death may have been from increased CSF pressure that can occur with N_2O anesthesia for air encephalography. Gordon and Greitz[11] state that "a combination of halothane and hypercarbia certainly has a far more significant intracranial pressure-elevating effect than nitrous oxide during pneumoencephalography."

In our series, the initial CSF pressure, taken 15 to 20 minutes after the induction of halothane-N_2O-O_2 anesthesia, was rarely elevated unless the patient's disease suggested the possibility of increased intracranial pressure. Our patients were carried on light anesthesia and kept hyperventilated. The closing pressures were never elevated within a few minutes after the injection of large volumes of N_2O contrast medium.

Jacoby and associates[12] consider air embolism as more likely to occur in children because a specified amount of gas will fill a larger portion of the ventricular system, and because needle placement is more difficult. During PEG fatal venous gas embolism has occurred with helium,[12] with air,[13] and with O_2.[14] Burko and Klatte[15] showed that dogs can withstand up to 5 times as much N_2O as air injected IV before succumbing. Paul[16] hypothesizes that a venous N_2O embolus with N_2O anesthesia would tend to be held in the gas phase and be "insoluble" because of the high N_2O partial pressure in venous blood. By ventilation with 100% O_2, however, nitrous oxide will be rapidly eliminated from the lung and then the venous blood, if cardiovascular integrity is present. The N_2O embolus rapidly decreases in size and becomes inocuous. Delayed gas embolism will not occur with N_2O because of the rapid loss of ventricular N_2O.

We experienced a venous N_2O embolus in a 2-week-old hydrocephalic infant undergoing ventriculography with N_2O contrast gas under N_2O-O_2 halothane anesthesia. After completion of a large ventricular injection, gas was noted in all the superficial scalp veins and a bradycardia began along with the characteristic murmur of air embolism. The patient was ventilated with 100% O_2, the murmur disappeared in 1½ minutes, and she recovered uneventfully.

Subdural hematoma and cardiovascular collapse[17] are suggested as possible neurologic complications of the rapid loss of CSF pressure when ventricular N_2O is eliminated. We had no patients in our series who exhibited either complication. Since we injected 2-4 times the amount of N_2O compared to CSF removed, our patients were faced with a less rapid decompression.

While most anesthetic administrations were uneventful some complications did occur. Extubation of the airway is a particular hazard in the mobile patient, and may occur in spite of adequate precautions. Short endotracheal tubes, failure of communication between anesthesia and radiologic personnel before required patient movement, spontaneous patient movement during the exam, and failure to adequately secure the endotracheal tube are all causes of extubation. Second-to-second monitoring of vital signs and close observation of the patient resulted in immediate recognition and reintubation. Severe bradycardia results from insufficient atropinization, too rapid contrast gas injection with sudden increased CSF pressure, and excessive anesthetic concentrations. If not recognized the bradycardia may result in severe hypotension and cardiac arrest. Our hypotensive episodes were transient and responded to positional change or reduction of the halothane concentration. No patients with postintubation croup were reintubated or tracheotomized and all responded to mist, steroids and IPPB with racemic epinephrine.

There were no fatalities in our series. It is likely the infant with the N_2O embolism would have succumbed if air had been used. Light halothane-N_2O-O_2 anesthesia has proven safe and effective when combined with N_2O encephalography. Strict attention to the details of anesthetic administration and airway management are necessary. So far as we know this is the first time the application of gas physics has been used to provide patients with postoperative pain relief.

REFERENCES

1. Saidman LJ, Eger EI II: Change in cerebrospinal fluid pressure during pneumoencephalography under nitrous oxide anesthesia. Anesthesiology 26: 67-72, 1965

2. Munson ES: Effect of nitrous oxide on the pulmonary circulation during venous air embolism. Anesth & Analg 50:785-793, 1971

3. Smith RM: Anesthesia for Infants and Children. Third edition. St. Louis, The CV Mosby Company, 1968, p 346

4. Leigh D, Belton MK: Pediatric Anesthesiology. Second edition. New York, The Macmillan Company, 1960, p 408

5. Aird RB: Experimental encephalography with anesthetic gases. Arch Surg 32:193-217, 1936

6. Newman H: Encephalography with ethylene. JAMA 108:461-465, 1937

7. Smith H, Crothers B: Subdural effusion after pneumoencephalography in children. Trans Am Neurol Assoc 74:101-104, 1949

8. Davidoff LM, Dyke CG: The Normal Encephalogram. Philadelphia, Lea & Febiger, 1951, pp 42-48

9. Schwab RS, von Storch TJC: Alterations of cerebrospinal fluid subsequent to pneumoencephalography. N Engl J Med 217:21-24, 1937

10. Grant FC: Ventriculography, review based on an analysis of 392 cases. Arch Neurol Psychiat 14:513-522, 1925

11. Gordon E, Greitz T: Effect of nitrous oxide on cerebrospinal fluid pressure during encephalography. Br J Anaesth 42:2-8, 1970

12. Jacoby J, Jones JR, Zeigler J, et al: Pneumoencephalography and air embolism: simulated anesthetic death. Anesthesiology 20:336-340, 1959

13. King AB, Otenssek FJ: Air embolism occurring during encephalography. J Nuerosurg 5:577-579, 1948

14. Coleman FC, Schenken JR, Abbott WD: Air embolism during pneumoencephalography. Am J Clin Pathol 20:966-969, 1950

15. Burko H, Klatte EC: Renewed interest in gases for contrast roentgenography. Am J Roentgenol 99:645-659, 1967

16. Paul W, Munson ES: Gas embolism during encephalography. Anesth & Analg 55:141-145, 1976

17. Collan R, Ivananien M: Cardiac arrest caused by rapid elimination of N_2O from cerebral ventricle after encephalography. Canad Anaes Soc J 16:519-524, 1969

PNEUMOPERITONEUM. Three adult patients developing free abdominal air and signs of a perforated viscus during positive pressure ventilation are described. Two received PEEP ranging between 10 and 15 cm water. Tidal volumes were about 1200 ml and peak inspiratory pressures were 50 to 61 cm of water. Fever and leukocytosis were present in all three patients. Two patients underwent negative exploratory laparotomies. It is speculated that air under positive pressure may enter perivascular lung tissue and find its way into the retroperitoneal space where subsequent rupture results in free abdominal air. Pneumoperitoneum secondary to air leak should be considered in patients receiving positive pressure ventilation and developing signs of perforated abdominal viscus. *(Stringfield JT, Graham JP, Watts CM et al: Pneumoperitoneum. A complication of mechanical ventilation. JAMA 235:744-746, 1976)*

The Effect of General Anesthetic Agents, Ouabain, and Aldosterone on Striated Muscle Contraction in Toad

L. AMARANATH, MD*
NIKAAN B. ANDERSEN, MD†
Cleveland, Ohio‡

Na^+ and K^+ transport, resting potentials, action potentials, and muscle contraction are interrelated in the excitation-contraction coupling process. Since anesthetics affect the electrogenic Na^+ transport mechanism in the toad bladder model and the coupled Na^+, K^+ transport in muscle, the authors tested the hypothesis that the effects of inhalation anesthetics on ion transport and muscle contraction are parallel. In this study, the effects were assessed of 4 inhalation anesthetics and, for comparison, the effects of ouabain and aldosterone, on contractions of toad sartorius muscle.

Cyclopropane, N_2O, ether, and halothane, as well as ouabain and aldosterone, increased twitch height in low concentrations. Halothane, ether, and ouabain decreased twitch height in high concentrations. The effect of cyclopropane and N_2O, ouabain, and aldosterone on muscle contraction closely paralleled their action on electrogenic Na^+ transport. This observation supports the hypothesis that the influence of these agents on muscle contraction is linked to the effect on active ion transport or that both effects are equally sensitive to anesthetic agents.

GENERAL anesthetics have been shown to stimulate or to inhibit active electrogenic Na^+ transport in toad bladder in concentrations used for clinical anesthesia.[1] Stimulation and inhibition have also been noted in the effect of anesthetics on the resting membrane potential and on the contraction of muscle. Cyclopropane, which stimulates Na^+ transport,[2] was found to increase the resting membrane potential[3] and enhance contractile force in striated muscle,[4] while halothane, which inhibits Na^+ transport, lowered the membrane potential[3] and decreased contractile force.[5,6]

Since Na^+, K^+ transport, resting membrane potentials, action potentials, and muscle contraction are related in excitation-contraction coupling,[7] we assumed that anesthetics have similar effects on active Na^+ transport in bladder and muscle[8] and hypothesized that the effects of inhalation anesthetics on muscle contraction and ion transport are linked. We, therefore, compared the effect of a series of anesthetic agents on contractions of toad sartorius muscle with effects on Na^+ transport in toad bladder.

The proposed hypothesis further suggests that nonanesthetics with strong effects on active Na^+ transport should also affect muscle contraction. Accordingly, we studied the effect of ouabain and aldosterone on toad sartorius muscle contraction and compared it with their well-known effects on Na^+ transport in toad bladder.[9,10]

*Assistant Professor.

†Professor and Associate Director (deceased).

‡Department of Anesthesiology, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106.

Paper received: 8/28/75

Accepted for publication: 11/5/75

METHOD

Toads, *Bufo marinus*, were pithed and muscle strips were isolated from the sartorius muscle. The strips, 1.5 cm long and 0.1 to 0.2 cm thick, were suspended at room temperature from a minimal-displacement pressure transducer in a sintered glass funnel that contained 60 ml of a toad salt solution:[11] NaCl 112 mM, KCl 1.9 mM, $CaCl_2$ 1 mM, $NaHCO_3$ 2.3 mM, and NaH_2PO_4 0.08 mM. The pH of 7.8 did not change during the experiment. The solution was aerated with O_2 and the chamber was continuously perfused with a fresh solution at a rate of 6 ml/min. The concentrations of the drugs to be tested were determined in pilot experiments, where we selected 3 concentrations of each compound that were multiples of each other, produced stimulation and, if possible, inhibition.

The muscle strips were electrically stimulated directly 5 times/minute with a supramaximal, 50 μsec impulse. The twitch was recorded and after stabilization the following agents were tested: cyclopropane 10, 40, and 80 vol %; diethyl ether 0.3, 0.6, and 1.2 vol %; N_2O 20, 40, and 80 vol %; halothane 0.3, 0.6, and 1.2 vol %; ouabain 10^{-12}, 10^{-9}, and 10^{-6} M; and aldosterone 10^{-7}, 10^{-6}, and 10^{-5} M. The anesthetics were delivered in O_2 from an anesthesia machine and the concentrations were assessed by gas chromatography. The solids were dissolved in toad Ringer's solution and added to the bathing solution by pipet. At the conclusion of the experiments, up to 3.5 μg/ml d-tubocurarine chloride was added to test the effect of neuromuscular blockade.

The drugs were added in increments and the concentration was increased when the resulting change in twitch response had been stable for 10 minutes. Each drug was tested 6 times in different muscle strips and the effect of each concentration was expressed as percent of control twitch height. Each experiment lasted about 2 hours. In the pilot experiments, we had ascertained that the twitch response in stabilized untreated strips did not change significantly during this period. Upon discontinuation of the inhalational anesthetics, twitch height returned toward control values.

The results were expressed as mean ± 1 SE and the significance of differences was assessed by Student's 2-tailed, unpaired *t*-tests.

RESULTS

Ether 0.3 and halothane 0.3 and 0.6 vol % increased twitch height ($p<0.01$) (table 1). With 1.2 vol %, both agents decreased twitch ($p<0.01$). Cyclopropane 10 and 40

TABLE 1
Effect of 4 General Anesthetic Agents on the Twitch Response in Toad Striated Muscle*

	Concentration, vol %	Water/gas†	Molarity in water	△ Twitch height, % of control	Value‡ *p*
Cyclopropane	10		1.1×10^{-3}	+31 ± 13.4	$p < 0.05$
	40	0.28	4.6×10^{-3}	+41 ± 10.0	$p < 0.01$
	80		9.3×10^{-3}	+12 ± 9.1	NS
N_2O	20		4.9×10^{-3}	0	—
	40	0.59	9.8×10^{-3}	+5 ± 1.2	$p < 0.01$
	80		1.9×10^{-2}	+10 ± 3.0	$p < 0.01$
Ether	0.3		3.7×10^{-3}	+10 ± 2.5	$p < 0.01$
	0.6	30	7.4×10^{-3}	+6 ± 5.0	NS
	1.2		1.4×10^{-2}	−14 ± 1.4	$p < 0.01$
Halothane	0.3		1.9×10^{-4}	+7 ± 1.5	$p < 0.01$
	0.6	1.58	3.9×10^{-4}	+8 ± 3.7	$p < 0.01$
	1.2		7.8×10^{-4}	−8 ± 1.4	$p < 0.01$

*Results are means of 6 experiments expressed as percent from control twitch height ± 1 SE.

†Ostwald solubility coefficient at room temperature. Larson CP Jr: Solubility and partition coefficients, Uptake and Distribution of Anesthetic Agents. Edited by EM Papper, RJ Kitz. New York, McGraw-Hill Book Company, 1963, pp 5-19.

‡Significance of mean differences assessed with Student's 2-tailed unpaired *t*-test.

NS = not significant.

TABLE 2

Effect of Ouabain and Aldosterone on the Twitch Response in Toad Striated Muscle*

	Concentration, M/L	△ Twitch height, % of control*	p value†
Ouabain	10^{-12}	0	—
	10^{-9}	$+6 \pm 2.5$	$p < 0.05$
	10^{-6}	-9 ± 1.0	$p < 0.01$
Aldosterone	10^{-7}	$+3 \pm 1.0$	$p < 0.05$
	10^{-6}	$+9 \pm 1.2$	$p < 0.01$
	10^{-5}	$+16 \pm 2.0$	$p < 0.01$

*Results are means expressed as percent change from control twitch height of 6 experiments ± 1 SE.

†Significance of the differences between the treated and control muscles as assessed by Student's 2-tailed, unpaired t-test.

vol % gave stimulation ($p<0.05$ and 0.01), while 80 vol % had a variable effect. N_2O 20 vol % had no effect, but 40 and 80 vol % gave dose-dependent stimulation ($p<0.01$).

Ouabain, 10^{-12} M had no effect, 10^{-9} M increased twitch height ($p<0.05$) and 10^{-6} produced inhibition ($p<0.01$) (table 2). Aldosterone 10^{-7}, 10^{-6}, and 10^{-5} M increasingly enhanced twitch height.

The presence of curare 3.5 μg/ml in no instance affected muscle response.

DISCUSSION

In this study we accepted changes in the recorded twitch height as a direct expression for changes in contractile force. According to the Hill model for muscle,[12] we assume that we saw changes in contractility of the contractile element, rather than the elastic elements, in toad striated muscle strips. Neuromuscular continuity did not influence the results, because the muscles were stimulated directly. Furthermore, curare failed to alter twitch response with or without anesthetics.

In accordance with other authors,[6] we found that anesthetics depress or stimulate muscle contraction, depending upon agent and concentration. Pollard and Millar[6] reported that ether in concentrations of about 2 vol % depressed directly-evoked twitches in rat diaphragm, that halothane gave transient stimulation in concentrations of up to 5 vol %, and that cyclopropane up to 75 vol % stimulated the muscle. In our experiments, the 4 anesthetics tested produced sustained stimulation below a certain concentration while high concentrations of ether and halothane produced inhibition. Presumably cyclopropane and N_2O would also have decreased twitch height had we been able to further increase the concentration of these agents and still supply an O_2 tension of 150 torr.

Data by Price and coworkers[13] suggest that halothane decreases frog sartorius muscle heat production at 0° C. However, Strobel[14] has confirmed our observation regarding halothane potentiation of twitch height in frog sartorius at 25° C. We, therefore, propose that anesthetics in low concentration stimulate muscle contraction and inhibit contraction at higher concentrations. Anesthetic dosage affecting twitch height bears no relationship to minimal anesthetic requirements in the toad.[15] Cyclopropane stimulated contraction well above minimal anesthetic requirements (9 vol %), while ether depressed contraction at an equally effective anesthetic concentration (1.6 vol %). Thus, we assume that the anesthetizing effect of these anesthetics is not related to their effect on contraction. The nonanesthetic agents, ouabain and aldosterone, also increase muscle contraction.

TABLE 3

Effect of 4 General Anesthetics,[15] Ouabain,[9] and Aldosterone[10] on Toad Urinary Bladder

	Concentration	△ Na^+ transport, % of control
Cyclopropane, vol %	10	$+46 \pm 15.7$
	40	$+60 \pm 6.6$
	80	-51 ± 18.2
N_2O, vol %	20	0
	40	$+21 \pm 6.3$
	80	$+41 \pm 20.2$
Ether, vol %	1.0	$+12 \pm 5.1$
	2.5	$+46 \pm 16.7$
	5.0	-12 ± 4.3
Halothane, vol %	0.2	$+31 \pm 14.3$
	0.3	-11 ± 11.5
	0.6	-16 ± 10.4
Ouabain, molar concentration	10^{-8}	+17
	10^{-7}	+8
	10^{-6}	+4
	10^{-5}	−24
Aldosterone, molar concentration	10^{-7}	0
	10^{-6}	+30
	10^{-5}	+50

*Means of 5 experiments ± SE. The results for ouabain and aldosterone are presented without statistical evaluation since they are calculated approximations from the literature.[9,10]

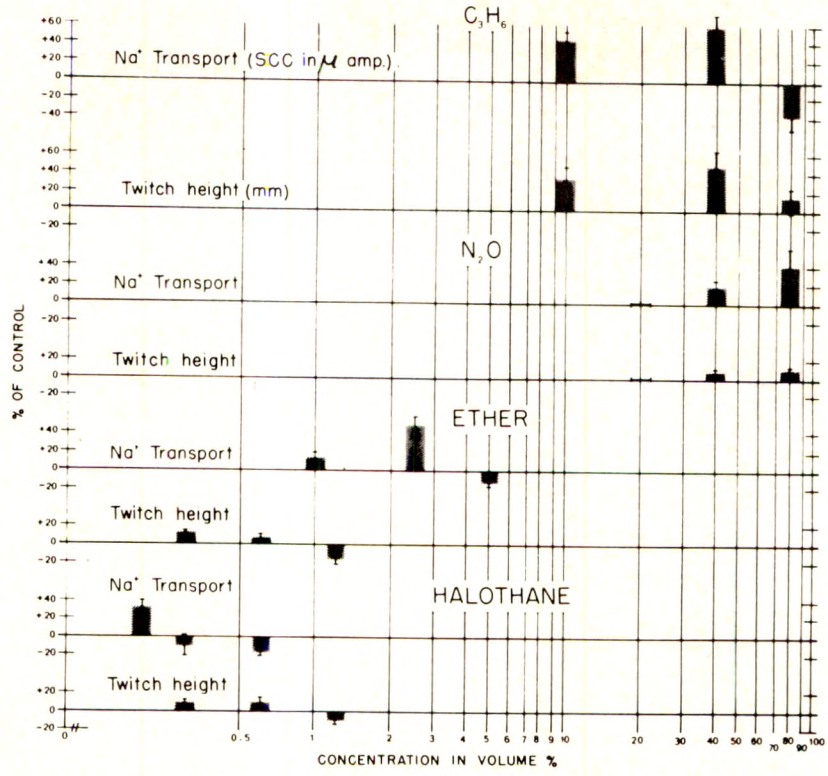


FIG 1. Effects of inhalation anesthetics on Na^+ transport[15] in toad urinary bladder and on twitch height in toad sartorius muscle. Vertical lines represent ± SE.

The relationship between the dose of the anesthetic and the electrogenic Na^+ transport has been studied previously.[1,2] Data from these studies and others involving ouabain and aldosterone are shown in table 3 and depicted, together with the present findings, in figures 1 and 2.

As can be seen, Na^+ transport in the toad bladder preparation was generally stimulated by low and depressed by high doses of all agents tested. The mechanical effects on striated toad muscle follow the same pattern of stimulation and then depression, but the two cannot readily be superimposed.

Aldosterone and ouabain are reported to stimulate and then inhibit Na^+ transport through mechanisms differing from those that apply for anesthetics. Ouabain presumably exerts its action through a direct effect on Na^+, K^+ ATPase,[9] aldosterone seems to stimulate metabolism,[10] and inhalational anesthetics probably depress transport through decreased permeability and stimulate transport through interaction with catecholamines.[2]

It may be a surprising coincidence that the anesthetic effects on muscle contraction in the toad are so closely paralleled by the anesthetic effects on the electrogenic Na^+ transport in the bladder, and that the effect of ouabain appears to run parallel to those of the anesthetics. The mechanism by which cardiac glycosides exert their positive inotropic effect is not fully elucidated. Investigators who focus on the glycoside effects on cation transport have postulated a

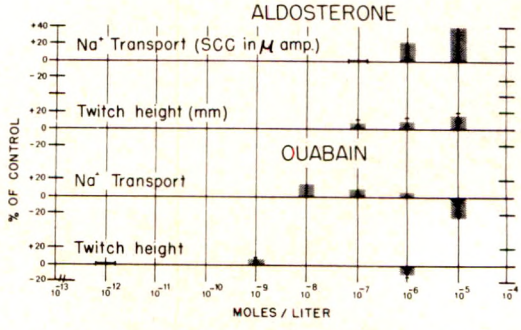


FIG 2. Effects of aldosterone[10] and ouabain[9] on Na^+ transport in toad urinary bladder and on twitch height in toad sartorius muscle. Vertical lines represent ± SE.

decreased Na^+ transport or increased Na^+ transport as possible explanations of the glycoside effect on contractility.[16]

Price[17] showed that "clinical concentrations" of halothane depressed myocardial contractility through an effect external to the contractile elements, possibly located in the cell membrane, with an effect on Ca^{++} availability to the contractile elements during the action potential. Our studies do not permit us to identify the mechanism by which Na^+ transport or twitch height was affected by the anesthetics and the nonanesthetic agents tested. The weight of the observations, however, suggests a membrane phenomenon as the common site of action.

The general "carrier" model for the metabolically mediated Na^+, K^+ membrane transport phenomena appears to be shared by toad bladder, muscle, and other cell membranes.[18] The effect of anesthetics on resting membrane potentials described by Kendig and Bunker[3] may be another expression of the relationship between anesthetic effects on Na^+, K^+ transport and muscle contractions. The effects on the membrane potential, of course, may be explained as hyper- or hypopolarization resulting from increased or decreased active Na^+, K^+ transport which, everything else being unchanged, would lead to changes in intracellular K^+ concentrations and the electrochemical K^+ gradient across the membrane, which is accepted as the main factor in the resting potential.[19]

Hodgkin and Huxley[20] demonstrated that the amount of Na^+ electrogenesis (Na^+ permeability during depolarization) depends on the resting membrane potential. If the resting potential is high, Na^+ electrogenesis will also be high and the activating system will be fully available.[21] Thus, anesthetics may increase twitch height by increasing the resting membrane potential and by making membrane depolarization more effective in activating the release of Ca^{++} to the contractile elements.

Our observations establish that anesthetics share effects on muscle contraction and ion transport with certain unrelated nonanesthetic agents. More work is needed to determine whether the active cationic transport phenomena in nonexcitable membranes resemble those in excitable membranes in their response to anesthetics, and whether anesthetics influence the contraction of muscle cells in part through their effects on transport phenomena.

ACKNOWLEDGMENT

The author (L.A.) is indebted to Dr. J. S. Gravenstein for his encouragement and assistance during the preparation of this manuscript.

REFERENCES

1. Andersen NB: Effect of general anesthetics on sodium transport in toad bladder. Anesthesiology 27:304-310, 1966

2. Andersen NB: Synergistic effect of cyclopropane and epinephrine on sodium transport in toad bladder. Anesthesiology 28:438-445, 1967

3. Kendig JJ, Bunker JP: Alterations in muscle resting potentials and electrolytes during halothane and cyclopropane anesthesia. Anesthesiology 36: 128-131, 1972

4. Sabawalla PB, Dillon JB: The positive inotropic action of cyclopropane on human intercostal muscle in vitro and its modification by d-tubocurarine. Anesthesiology 19:473-477, 1958

5. Sabawalla PB, Dillon JB: Action of volatile anesthetics on human muscle preparations. Anesthesiology 19:587-594, 1958

6. Pollard BJ, Millar RA: Potentiating and depressant effects of inhalation anaesthetics on the rat phrenic nerve-diaphragm preparation. Br J Anaesth 45:404-415, 1973

7. Taylor SR, Preiser H, Sandow A: Action potential parameters affecting excitation-contraction coupling. J Gen Physiol 59:421-436, 1972

8. Andersen NB, Amaranath L: Anesthetic effects on transport across cell membranes. Anesthesiology 39:126-152, 1973

9. McLane TK: A biphasic action of ouabain on sodium transport in the toad bladder. J Pharmacol Exp Ther 148:106-110, 1965

10. Crabbé J, DeWeer P: Action of aldosterone on the bladder and skin of the toad. Nature 202: 298-299, 1964

11. Mazzella H: The staircase phenomenon and distention of the myocardium on "Bufo arenarum hensel." Acta Physiol Lat Am 7:95-103, 1957

12. Hill AV: Heat of shortening and dynamic constants of muscle. Proc R Soc Lond (Biol) 126: 136-195, 1939

13. Price KA, Matsumoto Y, Frederickson EL: Effect of halothane on isometric twitch and tetanus response and the associated heat production in striated muscle of frogs. Anesth & Analg 54:527-535, 1975

14. Strobel GE Jr: Guest discussion. Anesth & Analg 54:535, 1975

15. Andersen NB, Shim CY: Sodium transport and anesthetic requirements in the toad. Anesthesiology 34:338-343, 1971

16. Schwartz A, Lindenmayer GE, Allen JC: The sodium-potassium adenosine triphosphatase: pharmacological, physiological and biochemical aspects. Pharmacol Rev 27:3-134, 1975

17. Price HL: Calcium reverses myocardial depression caused by halothane: site of action. Anesthesiology 41:576-579, 1974

18. Sjodin RA: Ion transport across excitable cell membranes, Biophysics and Physiology of Excitable Membranes. Edited by WJ Adelman Jr. New York, Van Nostrand Reinhold Company, 1971, pp 96-124

19. Lakshminarayanaiah N: Transport Phenomena in Membrane. New York, Academic Press, 1969, pp 375-376

20. Hodgkin AL, Huxley AF: The dual effect of membrane potential of sodium conductance in the giant axon of Loligo. J Physiol (Lond) 116:497-506, 1952

21. Weidmann S: The effect of the cardiac membrane potential on the rapid availability of the sodium-carrying system. J Physiol (Lond) 127: 213-224, 1955

HALOTHANE AND REDUCED HEPATIC BLOOD FLOW. The authors describe marked reductions in hepatic arterial flow during angiographic studies performed under halothane anesthesia. A 4-year-old female with neurofibromatosis undergoing a renal arteriogram was noted to have poor visualization of the hepatic arteries distal to the common hepatic artery and perfusion of the right liver lobe was minimal. In the previous 18 months this child had received four uneventful halothane anesthetics for nonabdominal procedures. A second patient (3-year-old female) manifested similar slowing of hepatic arterial flow which returned to normal 25 minutes after discontinuing halothane and substituting nitrous oxide and d-tubocurarine. Neither patient manifested clinical or biochemical evidence of postanesthesia liver dysfunction. A subsequent review of 25 aortograms performed with halothane anesthesia revealed slowing of hepatic arterial flow in 8 patients (32%). Halothane may produce an increase in vasomotor tone specific to hepatic circulation while sparing arterial flow to other abdominal viscera. The marked slowing of hepatic arterial flow by halothane may reflect increased vasomotor tone primarily at the hepatic arterial, sinusoidal or venous levels. *(Burger PE, Culham JAG, Fitz CR et al: Slowing of hepatic blood flow by halothane: Angiographic manifestations. Radiology 118:303-306, 1976)*

Methoxyflurane Biotransformation and Renal Function Following Methoxyflurane Administration for Vaginal Delivery or Cesarean Section

STEVEN R. YOUNG, MD*
ROBERT K. STOELTING, MD†
VIRGINIA K. BOND, MD‡
CHRISTINE PETERSON, RN§
Indianapolis, Indiana‖

Methoxyflurane (MOF) administration for conscious analgesia during vaginal delivery (range 5 to 70 min, mean 23 min) or for anesthesia following delivery of the infant at cesarean section (range 25 to 70 min, mean 44 min) was studied in 18 healthy parturients. Serum ionic fluoride increased significantly in both groups 2 hours after discontinuing MOF with peak concentrations of 11.2 and 14.1 μmol/L in the vaginal delivery and cesarean section groups, respectively. Individual peak serum ionic fluoride levels in the 2 groups of 21 and 25 μmol/L were well below reported levels for subclinical toxicity. Significant ionic fluoride elevations in fetal umbilical venous blood (mean 5.3 μmol/L) were measured in the vaginal-delivery group. Maternal urinary ionic fluoride and oxalate were elevated 24 and 48 hours postpartum. BUN, creatinine, urine volume, and urine osmolality remained within normal range. These data indicate that hazardous elevations of serum ionic fluoride with subsequent renal dysfunction are unlikely following low-dose MOF administration for vaginal delivery or cesarean section.

NUMEROUS reports have appeared documenting the association between methoxyflurane (MOF) biotransformation to ionic fluoride and oxalate and postoperative renal dysfunction.[1,2] Nevertheless, MOF administration during vaginal delivery or cesarean section provides good maternal analgesia without significant effects on uterine tone. Documentation that low-dose MOF administration does not result in hazardous serum ionic fluoride elevations would be useful. Indeed, large increases in serum ionic fluoride do not usually occur following awake MOF analgesia during labor and vaginal delivery.[3]

In the present study, MOF biotransformation and renal function were determined in two groups of healthy parturients who received MOF either for conscious analgesia during vaginal delivery only or after delivery of the infant at cesarean section.

METHODS

During vaginal delivery, 11 patients received pudendal nerve blocks and conscious

*Anesthesia Resident.
†Associate Professor of Anesthesiology/Pharmacology.
‡Director of Obstetrical Anesthesia; Assistant Professor.
§Anesthesia Research Nurse.
‖Department of Anesthesiology, Indiana University School of Medicine, Indianapolis, Indiana 46202.
This study was supported in part by a grant from Abbott Laboratories, North Chicago, Illinois.
Paper received: 7/7/75
Accepted for publication: 8/14/75

analgesia with MOF (0.2 to 0.5% Pentamatic® vaporizer settings) delivered in O_2, 5 L/min via a semiclosed-circle absorption anesthetic system. Administration was continuous or intermittent, as determined by the patient's ability to respond to verbal commands.

The second group of 7 patients for elective cesarean section received 4 mg/kg of thiamylal and 60% N_2O in O_2 plus succinylcholine for skeletal muscle paralysis until delivery of the infant. Following delivery, anesthesia was maintained with MOF (0.2 to 0.5% Pentamatic vaporizer settings) plus 60% N_2O at a total gas flow of 5 L/min via a semiclosed-circle absorption anesthetic system.

Mothers with renal or hepatic disease, preeclampsia, or history of drug intake (other than supplemental iron and vitamins) were excluded from this study.

Venous blood samples for serum ionic fluoride were obtained from all mothers before MOF administration (control), at delivery (vaginal delivery group), 1 hour after discontinuing MOF (cesarean-section group), and in all patients 2, 24, and 48 hours after MOF administration. Samples were also obtained from the umbilical vein of all infants in the vaginal-delivery group at the time of delivery. Serum creatinine, blood urea nitrogen (BUN), serum uric acid, and serum osmolality were determined before delivery and 24 and 48 hours postpartum. Ionic fluoride was measured with a fluoride ion-specific electrode.[4] Oxalate was measured by Bio-Science Laboratories.[5]

Umbilical vein and maternal arterial samples were collected in glass syringes at delivery and analyzed for MOF concentration by gas chromatography after extraction into tetrachloroethylene.[6]

Maternal 24-hour urine collections for ionic fluoride, oxalate, osmolality, and total volume were initiated at delivery and continued for 48 hours.

Newborn condition at birth was ascertained by 1 and 5-minute Apgar scores and by time to sustained respirations.

Data were analyzed by Student's *t*-test, $p<0.05$ being considered significant.

RESULTS

Maternal groups were similar with respect to age (mean 28 years) and weight (mean 68 kg). The average duration of MOF administration was different: 23 minutes (range 5 to 70) in the vaginal-delivery group and 44 minutes (range 25 to 70) in the cesarean-section group.

Serum ionic fluoride increased significantly in all patients following MOF administration (tables 1 and 2). Peak ionic fluoride levels were 11.2 ± 1.4 μmol/L and 14.1 ± 2 μmol/L at 2 hours after discontinuing MOF for vaginal delivery or cesarean section, respectively. Ionic fluoride concentrations decreased, but were still significantly elevated above control levels, 24 and 48 hours postpartum. In 2 of 7 patients following cesarean section, serum ionic fluoride concentrations 3 hours after discontinuing MOF were similar to the 2-hour determinations. This suggested that the serum ionic fluoride elevations after 2 hours accurately reflected maximum fluoride elevations in this group.

At vaginal delivery, fetal umbilical vein ionic fluoride concentrations were 5.3 ± 0.7 μmol/L compared with 7.1 ± 0.8 in the mothers. Maternal MOF concentrations following vaginal delivery were greater than the corresponding fetal umbilical vein concentration (2.1 ± 0.4 mg/100 ml versus 1.5 ± 0.3 mg/100 ml). These arterial values corresponded to alveolar concentrations equal to 0.025 vol/100 ml and 0.018 vol/100 ml, respectively, assuming a blood-gas partition coefficient equal to 13 for mother and infant.

Significant increases, although still within the normal range for our laboratory, were seen in BUN at 24 and 48 hours in the vaginal-delivery group and in serum creatinine at 48 hours in the cesarean-section group (table 1).

Urinary excretion of ionic fluoride and oxalate were maximally elevated on the 1st day following delivery in both groups (table 3). Maternal urine volumes and urine osmolality were within normal range 24 and 48 hours postpartum.

Apgar scores were greater than 7 and 8 after 1 and 5 minutes, respectively, in the vaginal-delivery group infants, except in one 1.8 kg infant whose scores were 5 and 8. Time to sustained respiration was less than 60 seconds in all infants.

DISCUSSION

Serum ionic fluoride levels capable of producing dose-related renal dysfunction after MOF administration have been documented

TABLE 1
Maternal Laboratory Values (Means ± SE)
(Numbers of Determinations in Parentheses)

Test	Control	Delivery
Serum ionic fluoride (μmol/L)		
Vaginal delivery	2.7 ± 0.3 (11)	7.1 ± 0.8 (10)*
Cesarean section	2.6 ± 0.6 (7)	
Serum creatinine (mg/100 ml)		
Vaginal delivery	0.65 ± 0.06 (10)	0.65 ± 0.06 (10)
Cesarean section	0.63 ± 0.04 (6)	
Blood urea nitrogen (mg/100 ml)		
Vaginal delivery	6.4 ± 0.6 (10)	6.0 ± 0.6 (10)
Cesarean section	7.3 ± 1.0 (6)	
Serum uric acid (mg/100 ml)		
Vaginal delivery	4.9 ± 0.3 (10)	4.9 ± 0.3 (10)
Cesarean section	4.9 ± 0.5 (6)	
Serum osmolality (mOsm/L)		
Vaginal delivery	265 ± 2 (10)	267 ± 3 (11)
Cesarean section	270 ± 5 (4)	
MOF (mg/100 ml—vaginal delivery)		
Maternal arterial		2.1 ± 0.4 (11)
Fetal umbilical venous		1.5 ± 0.3 (9)

*Significantly different from control measurement ($p<0.05$).

TABLE 2
Serum Ionic Fluoride Level After Discontinuing MOF
(μmol/L) (Means ± SE)

1 hour	2 hours	24 hours	48 hours
	11.2 ± 1.4 (11)*	5.6 ± 0.8 (11)*	4.0 ± 0.5 (11)*
13.9 ± 1.9 (7)*	14.1 ± 2.0 (7)*	8.3 ± 1.9 (7)*	6.2 ± 1.3 (6)*
		0.73 ± 0.05 (11)	0.77 ± 0.09 (11)
		0.81 ± 0.11 (7)	0.85 ± 0.09 (6)*
		8.4 ± 0.6 (11)*	9.0 ± 0.7 (10)*
		5.7 ± 0.6 (7)	7.2 ± 0.7 (5)
		5.7 ± 0.3 (11)	5.9 ± 0.4 (11)
		6.0 ± 0.6 (7)	6.0 ± 0.8 (7)
		270 ± 3 (11)	273 ± 3 (11)
		263 ± 3 (5)	269 ± 6 (5)

by Cousins and Mazze.[2] For example, peak serum ionic fluoride concentrations above 50 μmol/L may be associated with subclinical toxicity manifested by delayed return to maximum preoperative urine-concentrating ability and increased serum uric acid. Serum ionic fluoride concentration above 90 μmol/L may produce further evidence of renal dysfunction: polyuria, high serum osmolality, hypernatremia, and low urine osmolality.

In this study, maximum serum ionic fluoride elevations after conscious analgesia during vaginal delivery (11.2 μmol/L) or after short-term administration for cesarean section (14.1 μmol/L) were far below levels

TABLE 3
Maternal Urinalysis Results (Means ± SE)
(Number of Determinations in Parentheses)

Test	Hours after discontinuing MOF	
	24 hours	48 hours
Urinary ionic fluoride (μmol/L)		
Vaginal delivery	504 ± 55 (9)	350 ± 48 (9)
Cesarean section	2072 ± 775 (3)	908 ± 196 (3)
Urinary oxalate (mg/24 hr)		
Vaginal delivery	83.4 ± 16.1 (9)	54.5 ± 13.1 (9)
Cesarean section	69.5 ± 2.5 (2)	39.7 ± 37 (2)
24-hour urine volume (ml)		
Vaginal delivery	2999 ± 432 (10)	1853 ± 330 (10)
Cesarean section	2140 ± 360 (3)	1825 ± 25 (3)
Urinary osmolality (mOsm/L)		
Vaginal delivery	299 ± 38 (10)	386 ± 31 (10)
Cesarean section	442 ± 73 (3)	359 ± 18 (3)

associated with detectable renal dysfunction.[1,2,7] Indeed, the highest individual elevation in the group receiving conscious analgesia was 21 μmol/L (after 17 min of MOF administration), while 25 μmol/L was the highest single value reported in a cesarean-section patient (after a 50-min exposure).

Some patients with higher arterial MOF concentrations or longer periods of exposure actually had lower serum levels of ionic fluoride, suggesting individual variability of MOF biotransformation. As would be expected with a dose-related response, concentrations following more prolonged awake MOF analgesia (mean 127 min) for both labor and vaginal delivery were greater (21.9 μmol/L)[3] than those found in this study. Furthermore, 2 patients manifested concentrations above 50 μmol/L with this more prolonged administration.[3]

Blood urea nitrogen or serum creatinine increased ($p<0.05$) following MOF administration, but these elevations did not exceed the normal range. Similar changes were reported by Creasser's group,[3] but another report[8] did not show any increase in BUN after MOF analgesia. Some renal-function changes might not have been observed, since early MOF-induced renal dysfunction is a concentrating defect,[2] and specific stress for concentrating ability was not tested.

A maternal artery-umbilical vein MOF difference was present at vaginal delivery: 2.1 mg/100 ml maternal versus 1.5 mg/100 ml fetal. This fetal MOF concentration was not associated with fetal depression as measured by Apgar scores or time to sustained respirations. Other reports[3,9] have demonstrated that maternal artery-fetal umbilical vein MOF gradients diminish with more prolonged MOF administration.

Mean serum ionic fluoride in the fetal umbilical vein at delivery was 5.3 μmol/L, compared with a maternal level of 7.2 μmol/L. (Infants born to mothers with no MOF administered have mean serum ionic fluoride levels of approximately 1 μmol/L.)[3] Increased fetal serum ionic fluoride levels would most likely be the result of transplacental fluoride diffusion or the consequence of MOF biotransformation in utero, though the degree of biotransformation could be limited by poorly developed neonatal microsomal enzymes.[10] What effects increased ionic fluoride have on the immature kidney is largely unknown. Other studies[11,12] have found maternal and fetal serum levels of ionic fluoride similar to those in this report.

Urinary excretion of fluoride and oxalate reflected MOF biotransformation. Peak urinary excretion of fluoride (2072 μmol/L) and oxalate (83.4 mg/24 hr) seen on the 1st postpartum day was far below levels reported after more lengthy MOF anesthesia.[13,14]

We conclude that dangerous serum ionic fluoride elevations and subsequent renal dysfunction are unlikely when low-dose MOF is administered for conscious analgesia during vaginal delivery or for short durations

following delivery of the infant at cesarean section.

REFERENCES

1. Mazze RI, Trudell JR, Cousins MJ: Methoxyflurane metabolism and renal dysfunction: clinical correlation in man. Anesthesiology 35:247-252, 1971

2. Cousins MJ, Mazze RI: Methoxyflurane nephrotoxicity—a study of dose response in man. JAMA 225:1611-1616, 1973

3. Creasser CW, Stoelting RK, Krishna G, et al: Methoxyflurane metabolism and renal function after methoxyflurane analgesia during labor and delivery. Anesthesiology 41:62-66, 1974

4. Fry BW, Taves DR: Serum fluoride analysis with the fluoride electrode. J Lab Clin Med 75: 1020-1025, 1970

5. Fraser J, Campbell DJ: Indirect measure of oxalic acid in urine by atomic spectrophotometry. Clin Biochem 5:99-103, 1972

6. Jacobs ES: The gas chromatographic determination of halopropane in blood. Anesth & Analg 43:177-185, 1964

7. Taves DR, Fry BW, Freeman RB, et al: Toxicity following methoxyflurane anesthesia. II. Fluoride concentrations in nephrotoxicity. JAMA 241:91-95, 1970

8. Rosen M, Latto P, Asscher AW: Kidney function after methoxyflurane analgesia during labor. Br Med J 1:81-83, 1972

9. Siker ES, Wolfson B, Dubransky J, et al: Placental transfer of methoxyflurane. Br J Anaesth 40:588-592, 1968

10. Done AK: Developmental pharmacology. Clin Pharm 5:432-479, 1964

11. Fry BW, Taves DR: Maternal and fetal fluorometabolite concentrations after exposure to methoxyflurane. Am J Obstet Gynecol 119:199-204, 1974

12. Palahniuk RJ, Cumming M: Plasma fluoride levels following obstetrical use of methoxyflurane. Can Anaesth Soc J 22:291-297, 1975

13. Silverberg DS, McIntyre JW, Ulan RA, et al: Oxalic acid excretion after methoxyflurane and halothane anaesthesia. Can Anaesth Soc J 18:496-504, 1971

14. Cousins MJ, Nishimura TG, Mazze RI: Renal effects of low-dose methoxyflurane with cardiopulmonary bypass. Anesthesiology 36:286-292, 1972

50th Congress Report

March 14-18, 1976

Phoenix, Arizona

THE 50th Congress of the International Anesthesia Research Society, a long-planned, milestone celebration in our history, was held in Phoenix, Arizona, March 14-18, 1976.

The meeting was originally scheduled for Caesars Palace in Las Vegas, Nevada, but an unexpected labor strike there necessitated its move to the Hyatt Regency Hotel/Civic Plaza in Phoenix three days prior to the scheduled opening. We very much regret the inconvenience this caused to those who did attend, and the disappointment of those who could not. (For an "inside" view of the meeting transfer as well as "outside" reaction, see "Chronicle of the 50th Congress—Location Change" on page 428 and correspondence following.)

Fifty-seven papers encompassing the broad spectrum of anesthesiology were presented. For the first time, the program committee ran simultaneous sessions. We hope this new format, of simultaneous sessions, was acceptable and we would appreciate your comments.

Eighty-two technical and scientific exhibits, all interesting and educational, each manned by a knowledgeable attendant, provided a rich source of information.

Prizes were awarded to three of the scientific exhibits for their excellent presentation of their particular subject matter.

First Prize: *Obstetric Anesthesia and the Newborn,* Gerard W. Ostheimer, M.D., and associates, Boston Hospital for Women and Harvard Medical School.

Second Prize: *Anticholinergic Differences —A Matter of Safety,* Alon P. Winnie, M.D., University of Illinois Hospital.

Third Prize: *American Independence—Anesthesia or Anaesthesia? Bicentennial Observations,* Keith Murrin, M.B., and coworkers, University of North Carolina.

Dr. Leroy David Vandam, Professor of Anaesthesia, Harvard Medical School and Anesthesiologist-in-Chief of the Peter Bent Brigham Hospital, Boston, Massachusetts, presented the Eleventh Annual Becton-Dickinson & Company Oscar Schwidetzky Memorial Lecture entitled "On the History of Ideas in Anaesthesia." Dr. Vandam's

reputation filled the lecture hall with an expectant audience. They were well rewarded. His paper will appear in the July-August issue of this journal.

The Fourteenth Annual Baxter-Travenol Lecture entitled "Epidemiologic Answers to Laboratory Questions in Environmental Cancer" was delivered by Dr. Irving J. Selikoff, Professor of Medicine, Director, Environmental Sciences Laboratory, Mount Sinai School of Medicine, New York, New York. Dr. Selikoff is internationally known for his many contributions to environmental health, a subject of great importance to everyone. His very educated presentation provided valuable information on a subject about which too many of us know too little. This paper will appear in the September-October issue of *Anesthesia and Analgesia.*

Our well attended Golden Anniversary Commemorative Luncheon was held on Tuesday noon, presided over by Dr. Kenneth K. Keown, Chairman of our Board of Trustees. He introduced our guests, Dr. John Ditzler, President, American Society of Anesthesiologists, and Dr. John H. A. Lawrence, President, Canadian Anaesthetists' Society. Both Dr. Ditzler and Dr. Lawrence expressed their pleasure and carried friendly greetings to us from their respective societies.

Dr. T. H. Seldon, Member of the Board of Trustees of the International Anesthesia Research Society and Editor of *Anesthesia and Analgesia . . . Current Researches* presented a brief history of the Society pointing out that Dr. McMechan, Founder of this Society, and first Editor of *Anesthesia and Analgesia* and Mrs. McMechan probably have done more for our specialty than most of us will ever realize.

The highlight of the luncheon was a presentation by Dr. B. B. Sankey, our Executive Secretary, of a check for $10,000 to Dr. John Ditzler for the Committee on Research of the American Society of Anesthesiologists to commemorate the 50th Anniversary of the International Anesthesia Research Society. (See Correspondence on page 426.)

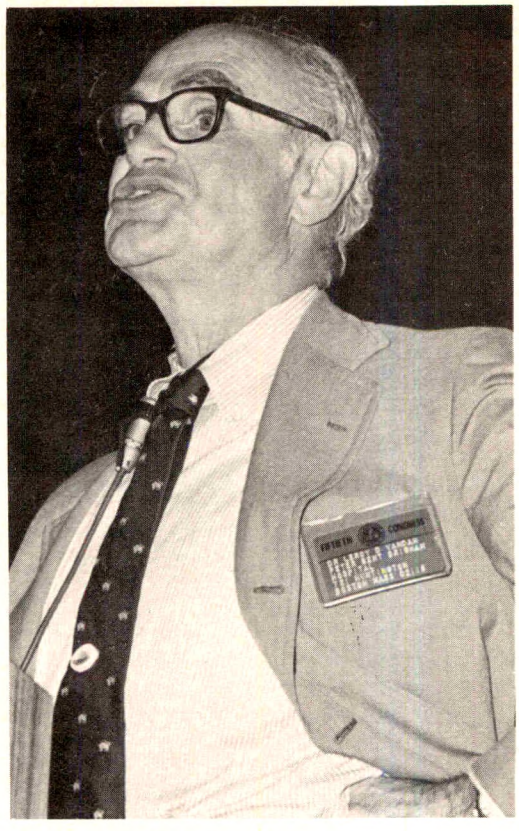
The members of the International Anesthesia Research Society are pleased to have participated in this gesture and look forward to seeing the results that follow the use of this money.

The Sunday evening social hour and the coke and coffee breaks during the scientific sessions again provided opportunities to renew old friendships, make new acquaintances, and discuss subjects of mutual interest.

The 51st Congress will be held at the Diplomat Hotel, Hollywood, Florida, on March 6-10, 1977.

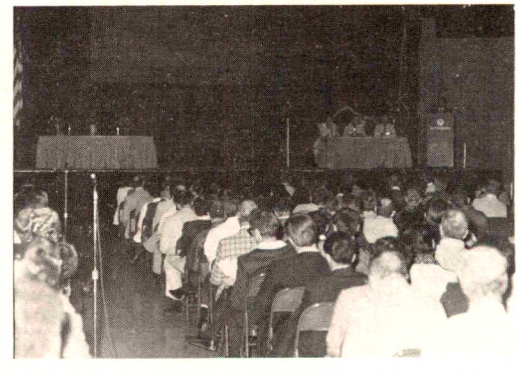
Titles and abstracts of papers to be considered for presentation must be in the hands of the program committee no later than August 2, 1976.

Abstract forms may be obtained from the Program Chairman, John T. Martin, M.D., Department of Anesthesiology, Medical College of Ohio, Toledo, Ohio.

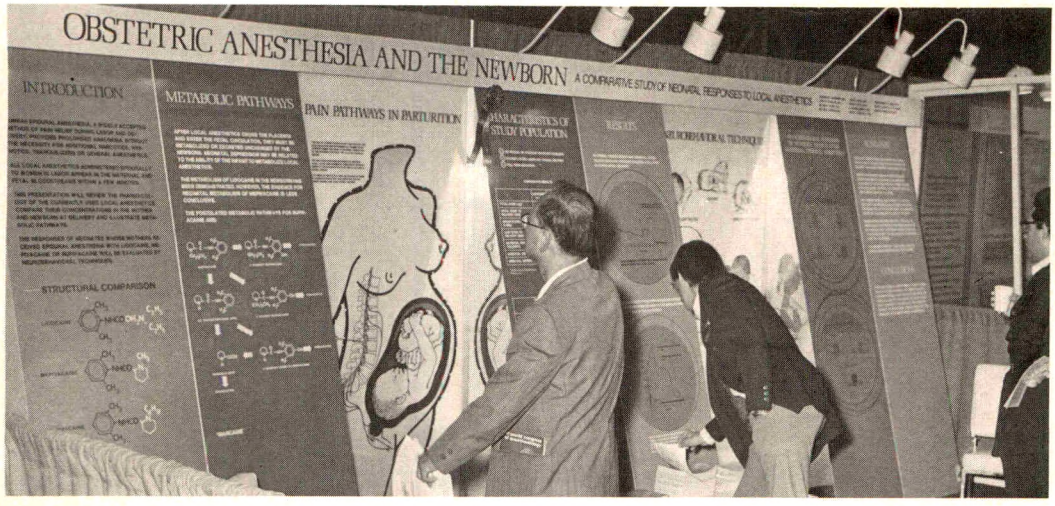


Dr. Leroy D. Vandam, was the Eleventh Annual Becton, Dickinson and Company Oscar Schwidetzky Memorial Lecturer. His presentation was entitled "On the History of Ideas in Anaesthesia."

Dr. Irving J. Selikoff, was the Fourteenth Annual Baxter-Travenol Lecturer. His presentation was entitled "Epidemiologic Answers to Laboratory Questions in Environmental Cancer."

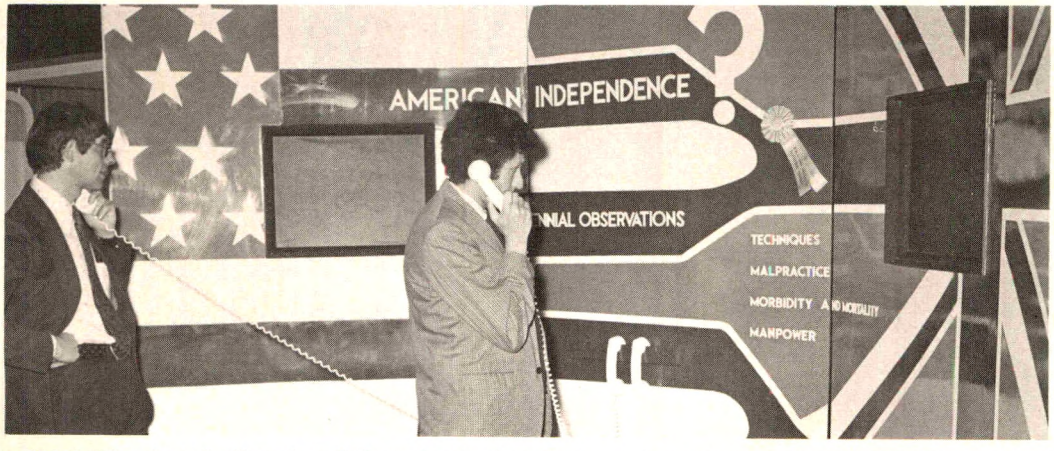


The Panel "Anesthesia for the Patient with Cardiac Disease" was well attended and very informative.



First Prize Award. "Obstetric Anesthesia and the Newborn." Gerard W. Ostheimer, MD and Associates.

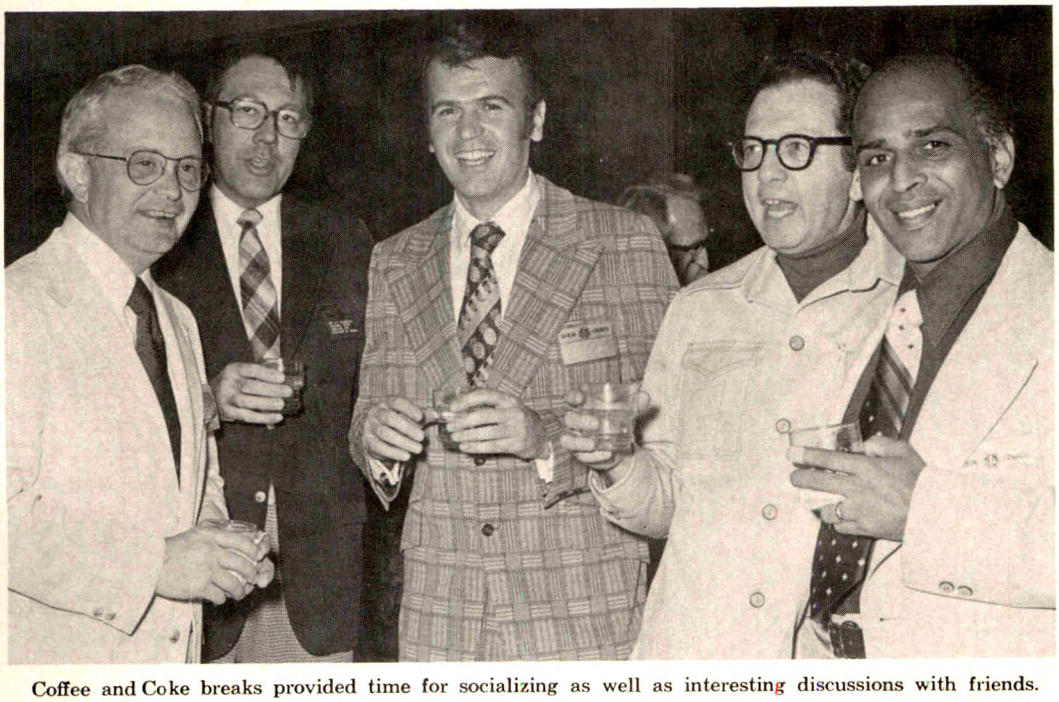
Second Prize Award. "Anticholinergic Differences —A Matter of Safety." Alon P. Winnie, MD.



Third Prize Award. "American Independence—Anesthesia or Anaesthesia? Bicentennial Observations." Keith Murrin, MB and Associates.

Sunday afternoon was a busy day for registration.

Intermission times were used to visit the technical and scientific exhibits.



Coffee and Coke breaks provided time for socializing as well as interesting discussions with friends.

Dr. B. B. Sankey, Executive Secretary of the International Research Society (right) presented a check for $10,000 for research to Dr. John Ditzler, President of the American Society of Anesthesiologists.

Kenneth K. Keown, M.D.
Chairman, Board of Trustees

Dear Doctor Keown:

This will officially acknowledge the receipt of the International Anesthesia Research Society's check in the amount of $10,000 made payable to the American Society of Anesthesiologists in behalf of its Committee on Research. It is my understanding that this is a commemorative donation in the interests of our mutual interest in research and the young investigators who produce the papers which appear from time to time on the IARS program as well as ASA. I am personally greatly appreciative of the confidence IARS has shown in ASA through this donation. I am particularly pleased that this donation could occur at a time when my life-long friend, Paul Dumke, was being honored in his final meeting as a Member of the Board of Trustees and when I was President of the ASA.

John W. Ditzler, M.D., President,
The American Society of Anesthesiologists

To the Board of Trustees and
Program Committee

Gentlemen:

I would like to thank the members of the Board of Trustees for the faith you have shown in the Committee on Research of the ASA by presenting them with the gift of $10,000. I am especially interested in this project, and feel that the future of anesthesia research is being developed at the present time and that this is one of the most efficient and effective ways that all of us can utilize to try to develop future investigators. The fact that the International Anesthesia Research Society felt that this would be an appropriate way to celebrate your fiftieth anniversary is to me a most significant milepost in the belief of a very outstanding group of people in the future of anesthesia research. You have my sincere and heartfelt congratulations, and my personal commendation for a significant contribution to the future of anesthesia research.

Evan L. Frederickson, M.D.
Professor
Anesthesiology and Pharmacology
Emory University
Atlanta, Georgia

Kenneth K. Keown, M.D.
Chairman, The Board of Trustees

Dear Ken,

Never have I witnessed or, for that matter, ever heard of a munificent gift on the order of that from the International Anesthesia Research Society to the American Society of Anesthesiologists. What a grand and generous thing to do!

Please accept from me the gratitude of the Scientific Council of the ASA for this magnificent gesture from one great organization to another.

Robert T. Patrick, M.D.
Vice President for Scientific Affairs
The American Society of Anesthesiologists

Chronicle of the 50th Congress
Location Change
March 7-14, 1976

LAS VEGAS' legendary Jimmy the Greek is probably thanking his lucky vegas that he didn't make "book" on the strike that moved the 50th Congress from his domain in Las Vegas to Phoenix, Arizona, to say nothing of quoting odds on the same meeting being "struck out" twice in the same city by the same union. Happen it did, however, and despite the fates that conspired against us, the meeting opened on schedule at 1 p.m. on Sunday, March 14th, and it turned out to be not only the sentimental milestone we had planned, but also a small psychological triumph.

For the many who were amazed and gratified at the expeditious transfer, this chronology of the "week that was" will be interesting. For those who expressed dismay at our "inept" handling of the move, it will hopefully result in a more understanding appraisal of the sequence and timing of events that made it necessary.

The story properly begins in March 1973 when the Las Vegas culinary workers signed a 3-year agreement which included a "no-strike" clause. With that assurance in hand (having had to move our 1970 meeting from Caesars Palace to Palm Springs, California, because of their strike), we finalized the 1976 meeting dates with Caesars Palace.

From that time on, in our many contacts with the hotel, numerous local suppliers and the Convention Bureau, there was not a single hint of a labor problem. We had worked long and hard to make our Golden Anniversary meeting the biggest and best in our history, and on Friday, March 5, when the final programs, preregistration cards and the last of our meeting supplies were shipped from Cleveland to Las Vegas, all systems were GO!

Sunday, March 7th: The first clue comes in an 11 p.m. telephone call to Dr. Seldon in Rochester from Dr. F. Ervin King, an IARS member from Missoula, Montana. He wondered if we still planned to meet in Las Vegas in view of the "probable" strike scheduled for Wednesday, March 10th, by the culinary workers' union. Dr. King's information came from a pediatrician friend in Las Vegas who heard it from the mother of a patient he had recently treated who had a relative in the union. Dr. Seldon immediately relayed the "message from Missoula" to Dr. Sankey in Cleveland, who in turn called the Caesars Palace management—2 a.m. on Monday, March 8th, Las Vegas time. They confirm the expiration of the culinary workers' contract at midnight on Wednesday, but are certain that even if the union turn down the offered contract, they would abide by the no-strike provision while they continued negotiations. So much for the "message from Missoula."

Monday, March 8th—6 a.m. Cleveland. Despite last night's reassuring comments from the hotel and the strong belief (hope?) that it couldn't possibly happen again, nagging memories of the 1970 strike that forced our move to Palm Springs are stirred. "Just in case," Dr. Sankey lists possible alternate meeting sites within a day's trucking distance of Las Vegas (so exhibits could be

moved). First on the list is Palm Springs, our 1970 port in the storm, and he reaches for the telephone which will soon feel like a permanent attachment. Hotel space we needed is not available, and Palm Springs is crossed off. Los Angeles is eliminated next —they have rooms but not adjacent exhibit space. San Diego can take us on March 21st but not on the 14th. Phoenix is last on the list. With a brand new hotel across the street from their Civic Center, they are ready, willing and able to take us if need be. We promise to advise them one way or another at midnight on Wednesday when we hear from Las Vegas. The Board of Trustees of the IARS is advised for the first time, and all of them book alternate travel to Phoenix.

Tuesday, March 9th: Several talks with the Las Vegas Convention Bureau and Caesars Palace management reveal no progress in negotiations. Neither would even speculate on the chances of a strike, but we detect, for the first time, some reservation that the no-strike clause would prevail.

Pending the union decision the next day, we alert all program participants and technical and scientific exhibitors that we may have to move the meeting to Phoenix. If we have to move, we need to know whether the many participants are willing to go along. The overwhelming majority are. Principals of the American Society of Regional Anesthesia, whose inaugural meeting is to follow ours, also are advised. They, too, will "roll with the punches."

The Las Vegas exhibit drayage and decorating contractors are requested to make contingency plans to move and set up exhibits in the Phoenix Civic Plaza.

Since our meeting preregistration cards are already on a truck enroute to Las Vegas, we cannot plan to advise registrants if the meeting is changed. Caesars Palace readily agrees, if necessary, to send telegrams to meeting registrants with reservations at their hotel and to the overflow registration at the MGM Grand hotel.

Wednesday, March 10—midnight in Las Vegas, Thursday, March 11—3 a.m. in Cleveland. Caesars Palace advises that the union vote on the new contract has been postponed until after negotiations are resumed twelve hours later. The hotel feels the situation is serious, but not altogether impossible. In the absence of a clear-cut union decision, the burden is completely on us. H-Hour is here! The consensus after several telephone calls to IARS Board members is: we are determined to hold the 50th Congress so we must move to Phoenix. More telephone calls and all the prearranged contingency procedures are implemented. Six hours later the IARS staff is in the air to Phoenix with 72 hours remaining to revamp our meeting plans and start from scratch with 2 hotels and a separate convention center we had never seen.

Thursday, March 11th—2:30 p.m., Phoenix. Initial misgivings and anxiety give way to relief as the IARS staff is greeted by the Phoenix Convention Bureau staff and taken directly from the airport to a meeting with an enthusiastic delegation from the hotels, civic center and service and supply firms whose assistance is essential to salvaging our meeting. Their sincere interest, concern and know-how is reassuring. We begin to see a rainbow in the Valley of the Sun!

Friday, March 12th: In Las Vegas: The culinary workers vote to strike. Ironically, we are now grateful to them for two reasons. First, the national news coverage will reach the registrants we were unable to contact directly. And, since the decision to move was made before the strike was voted, we now assume the role of foresighted planners —much nicer than the best of the possible alternatives.

The last of five double trucks containing the technical and scientific exhibits is loaded and starts the 250-mile haul to Phoenix. We calculate the cost and are temporarily anesthetized. What price determination! *In Cleveland:* The IARS office telephones are ringing off the hook as the meeting change telegrams are being received all over the country. Unfortunately, the news coverage of the strike has not reached some areas— and is sketchy and confusing in others. Many of the callers are understandably upset and baffled. They're not happy—but "Ma Bell" has no complaints.

In Phoenix: The contract is signed with the Civic Center for meeting and exhibit space; audio-visual equipment is ordered; social functions arranged with the Hyatt Regency; airlines contacted and urged to supplement scheduled service in and out of Phoenix; news services contacted to publicize the Las Vegas strike and our move to Phoenix; housing and reservation details

coordinated with cooperating hotels, who are now checking in the first of our registrants. Caesars Palace management personnel arrive mid-afternoon with a station wagon full of IARS convention supplies, including vital preregistration cards. We are relieved to find everything has come through except the Golden Anniversary souvenir pens. (They finally arrived on Wednesday, the second last day of our meeting.)

Saturday, March 13th: Six registration clerks from the Phoenix Chamber of Commerce assist in embossing, typing and stuffing badges for 1700 preregistrants, including spouses and exhibitors. On completion at 9:30 p.m. there is much speculation on the number of badges that would be picked up.

Exhibit trucks arrive in Phoenix and are uncrated in the Civic Plaza. When the last exhibit is assembled on Sunday afternoon, all are present and accounted for except one —Dr. T. J. Akamatsu's "Ketamine for Parturition" scientific exhibit is missing. It is located two days later—in Reno of all places.

Many more check-ins at the Hyatt Regency and the Adams Hotel. It's working!

Sunday, March 14th: Registration opens on schedule at 1 p.m. and immediately takes on the aura of an army reunion. The "survivors" straggle in with assorted tales of relief, amazement and woe. Someone suggests we attach purple hearts to the gold badges. The bouquets take a decided lead over the brickbats, and we maintain an anxious vigil over the badges that still need to be claimed. Around 4:30 p.m., Dr. Anis Baraka, a program participant from embattled Beirut, Lebanon, checks in and is greeted like a conquering hero. He is amazed at the fuss. "You think you have problems? When I left Lebanon last night, we had two presidents and two armies." At that point, we didn't know whether to laugh or cry with him, but we knew one thing for sure: It had been a "gutsy," hectic, uphill and expensive week for us, and even if nobody else shows up, it was all worth it. The 50th Congress was alive and well—and open for business.

Miss Dorothy Merich,
IARS Cleveland Office

Mrs. Agnes M. Osborn,
Rochester Editorial Office

EPILOGUE

The final program of the meeting included this sentence: "That the 50th Congress is being held today is indeed a monument to the continued vitality of the specialty which supports it." When that was written we had no idea how truly prophetic it was. No matter how determined we were that it would take place, it couldn't have happened without an equal commitment from our members. When we closed the meeting on Thursday, March 18th, we found that professional registration totaled 825 out of 977 pre-registered. Total meeting registration was 1425 vs 1700 preregistered. Another national meeting, also displaced by the Las Vegas strike preregistered 2000 and ended up with 800 attending. We can add nothing to the comparison except our warm appreciation for the wonderful support.

We are especially grateful to Dr. King whose distant early warning from Missoula quite possibly saved the day. We subsequently learned that a commitment was sought for the Phoenix space that we used just five hours after we had secured it.

Outside of the specialty there were a great many others whose interest, concern and hard work were invaluable and should be noted:

Charley Monahan and Bill Tobin of Caesars Palace Hotel for their wholehearted cooperation in effecting the transfer; Ted Sprague, Pam Cash and their numerous assistants at the Phoenix and Valley of the Sun Convention Bureau for their round-the-clock, enthusiastic response to our SOS; Wally Oberlender and his staff at the Hyatt Regency and Ron Lindemann and the Adams Hotel personnel for their efficient handling of our meeting needs and the many courtesies extended to our registrants; Charles B. Slack and the staff of our exhibit management company for their extra efforts and cooperation in overseeing this aspect of the meeting transfer; Denny Maus and the employees of the Phoenix Civic Plaza who were unfailingly cooperative in providing for our meeting needs; Dr. Brian Lockwood at the St. Luke's Medical Center in Phoenix for loaning us some of their audio-visual equipment not otherwise available in the area.

To all of them, our sincere thanks and appreciation.

For the IARS Board of Trustees,
Kenneth K. Keown, M.D., Chairman;
Emerson A. Moffit, M.D., Vice Chairman;
and B. B. Sankey, M.D., Executive Secretary.

To the Board of Trustees and Program Committee:

I want to congratulate you and your staff for successfully moving the International Anesthesia Research Society Meeting so smoothly from Las Vegas to Phoenix. Everyone was amazed at the painless, effective transition.

Also, I would like to comment upon two significant events at the Fiftieth Congress of the International Anesthesia Research Society. I thought the $10,000 contribution to the ASA for furthering research was generous and is certainly timely. I think the change in format to running simultaneous presentations did successfully enhance the value of the meeting by broadening the scope of presentations and increasing the number of worthwhile papers.

J. G. Reves, MD
Department of Anesthesiology and
Pharmacology
University of Alabama Medical Center
Birmingham, Alabama

To the Board of Trustees and Program Committee:

I would like to express my appreciation for the great effort and excellent performance which occurred in transferring our 1976 meeting from the scheduled site in Las Vegas to the actual site, Phoenix, Arizona. The smoothness and efficiency with which this change was implemented stands as a tribute to both the Board of Trustees and the Program Committee and indicates that our society remains active, useful and responsive to the needs of its membership. I feel privileged to be counted as a member.

Edward A. Brunner, MD, PhD
Department of Anesthesia
Northwestern University
The Medical School
Chicago, Illinois

50th Congress Technical Exhibitors

A note of thanks to the following 63 companies for their support of our Golden Anniversary meeting. Despite the confusion and inconvenience of the last-minute move from Las Vegas to Phoenix, 58 of the exhibits were staffed and "open for business" to a most appreciative audience. The I.A.R.S. Board of Trustees is especially grateful for their understanding cooperation.

Abbott Laboratories
Air Products and Chemicals, Inc.
Air Shields, Inc.
Allergan Pharmaceuticals
American Optical Corporation
Anesthesia Associates, Inc.
Anesthesia Medical Specialties
Applied Medical Research Corporation
Astra Pharmaceutical Products, Inc.
Audio-Digest Foundation
Ayerst Laboratories
Becton-Dickinson,Division of Becton, Dickinson and Company
Bivona Surgical Instruments, Inc.
Bourns Life Systems
Burroughs Wellcome Co.
Cal-Med Electronics Co.
Cavitron/KDC Medical Sales A Division of Cavitron Corporation
Chemetron Medical Products Division
Concept, Inc.
Cook Incorporated
Cyprane North America, Inc.
Datascope Corp.
Deseret Pharmaceutical Co., Inc.
Devices Limited, Instrument Division
Diamed, Division of Illinois Tool Works Inc.
Dupaco, Incorporated
Elsevier/Excerpta Medica/North-Holland
J. H. Emerson
Encyclopaedia Britannica Inc.
Extracorporeal Medical Specialties, Inc.
Fenwal Laboratories
Harris-Lake, Inc.
International Biophysics Corporation
Jelco Laboratories
K & G Healthcare Industries Anesthesia Division
Liquid Carbonic Corporation
McNeil Laboratories, Inc.
Medsonics, Inc.
Monitrode, Inc.
National Catheter Corp.
North American Drager
Ohio Medical Products
Organon Inc.
Pall Biomedical Products Corp.
Parke, Davis & Company
Penlon Inc.
Perkin-Elmer Corporation
Pfizer Laboratories
Pharmaseal Laboratories
Professional Educational Aids
A. H. Robins Company
Royale Laboratory
Rusch Inc.
W. B. Saunders Co.
Surgikos, A Johnson & Johnson Company
Tektronix, Inc.
Travenol Laboratories, Inc.
Vital Signs, Inc.
Williams & Wilkins Company
Winthrop Laboratories
Wyeth Laboratories
Xomed

Case History Number 90:

Cardiac Decompensation During Enflurane Anesthesia in a Patient with Myotonia Atrophica

MICHAEL B. MEYERS, MD*
PAUL G. BARASH, MD†
New Haven, Connecticut‡

THE patient, a 43-year-old, 83 kg man, was admitted to the hospital with the chief complaint of nonradiating right upper quadrant and midepigastric tenderness. Physical findings consistent with myotonic dystrophy, noted 4 years before, were also present at this admission.

Vital signs and laboratory data, including hemogram and liver profile, were normal. Serum K^+ was 3.3 mEq/L (normal = 3.6 to 5.5 mEq/L); other serum electrolytes were within normal range. Chest x-ray was normal and ECG demonstrated a 1st-degree heart block. Arterial blood gases (F_{IO_2} = 0.21) were: pH 7.56, P_{aCO_2} 22 torr, P_{aO_2} 76 torr.

On the 4th hospital day, the patient was premedicated with 10 mg of morphine sulfate, 100 mg of secobarbital, and 0.5 mg of atropine IM. One hour later, on admission to the operating room for cholecystectomy and common bile duct exploration, his vital signs were arterial blood pressure (BP) 130/90 torr, pulse 80 bpm and respirations 15/minute. Anesthesia was induced with 180 mg of thiopental IV and N_2O (70%) in O_2 supplemented with enflurane (2% inflow concentration into the circle system). The trachea was intubated without the use of muscle relaxants.

Following induction, anesthesia was maintained with N_2O (60%) in O_2 with enflurane (2%). Ten minutes later under controlled ventilation, the pulse rapidly decreased to 70 bpm and systolic BP decreased to 50 torr. The patient was given 0.5 mg of atropine IV without response. Enflurane was discontinued and 30 mg of mephentermine IV was administered in divided doses. Within 1 minute, the BP rose to 150/90 torr and pulse to 110 bpm. A radial artery catheter and pulmonary artery flow-guided catheter were introduced percutaneously.

Pulmonary capillary wedge pressure was 10 torr and cardiac output was 5.2 L/min (thermodilution). Arterial blood gases (F_{IO_2} = 0.5) were: pH 7.40, P_{aCO_2} 29 torr, P_{aO_2} 70 torr. The pulmonary capillary wedge pressure remained stable for 90 minutes. Lactated Ringer's solution was infused at a rate of 8 to 10 ml/kg/hr during the first 90 minutes.At this time, the ECG recorded a right bundle branch block and the pulmonary capillary wedge pressure was noted to have increased to 22 torr (BP 110/60 torr). Arterial blood gases (F_{IO_2} = 0.5) were: pH 7.59, P_{aCO_2} 19 torr, and P_{aO_2} 87 torr. Cardiac output was 4.5 L/min. Following furosemide (40 mg IV), the pulmonary capillary wedge pressure returned to

*Resident.
†Assistant Professor.
‡Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut 06510.
Reprint requests to Dr. Barash.

This feature was conducted by Edwin S. Munson, Associate Editor, Professor, Department of Anesthesiology, University of Florida College of Medicine, Gainesville, Florida 32610.

12 torr (BP 120/70) during the next 30 minutes. The remainder of the 4-hour anesthetic procedure was uneventful.

At the completion of the operation, the patient was admitted to the Surgical Intensive Care Unit (ICU), where ventilation was assisted by a volume-limited ventilator. A 12-lead ECG recorded a right bundle branch block with anterior T wave inversion, which was interpreted as either "secondary to the right bundle branch block or ischemia." Postoperative chest x-ray was within normal limits. Cardiac output was 9.5 L/min, pulmonary capillary wedge pressure was 5 torr, and BP was 170/90 torr. Three hours later, tracheal extubation was accomplished and 40% O_2 given by mask.

On the 1st postoperative day, the patient's condition was stable. The ECG revealed disappearance of the right bundle branch block and T wave inversion with return to preoperative 1st-degree heart block. He was discharged from the ICU after 3 days and from the hospital 15 days postoperatively.

DISCUSSION

Myotonic dystrophy is associated with unexpected perioperative morbidity and mortality.[1] Although there are numerous studies of respiratory function pertaining to operative management, there has been little focus on the cardiovascular stability of these patients in the anesthetized state.

Cardiac abnormalities are becoming increasingly appreciated in this disease as a concomitant to the skeletal muscle disorder.[2] Although cardiac manifestations usually occur relatively late in the course of the disease, they may precede clinical recognition of the primary disease process.[3] The ECG most commonly reflects conduction abnormalities, i.e., atrioventricular delay and/or aberrant intraventricular impulse propagation.[4] Disturbances of rhythm, especially bradycardia, are frequently noted.[5] Furthermore, ECG and vectorcardiographic (VCG) changes simulating myocardiac infarction have been reported.[6,7]

Cardiac catheterization in unanesthetized patients has revealed elevated right ventricular, pulmonary artery diastolic and pulmonary capillary wedge pressures.[8,9] To our knowledge, there has been no prior report of abnormalities of pulmonary artery pressures in the anesthetized subject. There is little correlation between the extent of musculoskeletal impairment and cardiovascular reserve in these patients. The etiology of the cardiac dysfunction has been theorized to be a genetically determined biochemical abnormality,[5] a degenerative cardiomyopathy,[10] or a combination of the latter with ventilatory insufficiency.[8] Fearrington and associates[7] hypothesized that sudden death, which is common in myotonic dystrophy, may be due to cardiovascular causes secondary to the cardiomyopathy seen in over 50% of cases studied at autopsy.

Preoperatively, the ECG, exercise testing, and VCG can be used to evaluate these patients. Continuous intraoperative and postoperative monitoring of the ECG and arterial BP is recommended. Since these patients can have associated degenerative cardiomyopathy, it is reasonable to assume they may exhibit varying degrees of left ventricular dysfunction. Thus, in addition, pulmonary artery pressure monitoring should be considered, since left ventricular dysfunction may elude clinical or laboratory detection.

REFERENCES

1. Kaufman L: Anesthesia in dystrophica myotonia. Proc Roy Soc Med 53:183-188, 1959

2. Petkovich NJ, Dunn M, Reed W: Myotonia dystrophica with A-V dissociation and Stokes-Adams attacks: a case report and review of the literature. Am Heart J 68:391-396, 1964

3. Hold JM, Lambert EHN: Heart disease as the presenting feature in myotonia atrophica. Br Heart J 26:433-436, 1964

4. Fisch CD: The heart in myotonica dystrophica. Am Heart J 41:525-538, 1951

5. Payne CA, Greenfield JC Jr: Electrocardiographic abnormalities associated with myotonic dystrophy. Am Heart J 65:436-440, 1963

6. Wenger NK: Myocardial involvement in systemic disease, The Heart. Edited by JW Hurst, RB Logue. New York, McGraw-Hill Book Company, 1969, pp 1238-1239

7. Fearrington E, Gibson TC, Churchill RE: Vectorcardiographic and electrocardiographic findings in myotonia atrophica. Am Heart J 67:599-609, 1964

8. Kilburn KH, Eagan JT, Sieker HO, et al: Cardiopulmonary insufficiency in myotonic and progressive muscular dystrophy. N Engl J Med 261: 1089-1096, 1959

9. Bashoar F, Winchell P, Reddington J: Myotonia atrophica and cyanosis. N Engl J Med 252: 768-770, 1955

10. Fisch C, Evans PV: The heart in dystrophica myotonia: report of an autopsied case. N Engl J Med 251:527-529, 1954

Comment

EDWIN S. MUNSON, MD

The cardiorespiratory abnormalities associated with the muscular dystrophies are of particular concern to the anesthesiologist. Last year, an article in this Journal by Ravin and colleagues (Anesth & Analg 54:216-218, 1975) discussed the anesthetic management of such patients and emphasized the increased sensitivity of the respiratory system to anesthetic agents. Although cardiac arrhythmias, ECG abnormalities, and even sudden death have been observed for over half a century, few reports of cardiac complications have appeared in the anesthetic literature.

This month's Case History represents a well-documented report of cardiac decompensation during enflurane anesthesia. This case history discusses various aspects of the cardiac pathophysiology and gives recommendations regarding the clinical management of myotonia atrophica patients.

Comment

GEORGE M. SAVIELLO, MD
Department of Anesthesiology
University of Florida
Gainesville, Florida

It has long been known that the cardiovascular system may be involved in myotonic dystrophy. Since the first report in 1912 of marked bradycardia and irregular cardiac action, there have been several reports concerning involvement of the cardiovascular system.[1] The incidence of ECG abnormalities ranges from 40 to 70 percent.[2,3] The principal abnormality detected has been an alteration of the P-R interval, mainly some variety of heart block. This alteration in the ECG is frequently present in the absence of any clinical symptoms. It has, in fact, been the means of diagnosis of an early case of myotonic dystrophy.[3]

There have been few reported cases of clinicopathologic correlation between the ECG and autopsy specimens.[4,5] Of these few, it appears that an infiltrative process of some type is responsible for the conduction defects. Coronary vasculature appears to be fairly well maintained. This causes a cardiomyopathy, frequently observable on VCG, and very often neglected clinically.

It is well established that these patients may have significant respiratory problems due to myotonia and muscle wasting.[6] It is now also obvious that they may have significant cardiovascular problems, with minimal or absent symptoms and laboratory evidence. Perhaps the reason these patients do not get into trouble is that muscle weakness limits activity and strain on the cardiovascular system.

Such patients must be anesthetized with extreme care. Careful attention should be paid to ventilation and airway management, and postoperative mechanical ventilation must be available. It would be prudent to assume that all patients have some degree of cardiomyopathy. Therefore, a technic should be used which has minimal effects upon the cardiovascular system. The potent inhalational agents with their myocardial-depressant properties should be avoided; a "balanced" N_2O-O_2 anesthetic, supplemented with narcotics to avoid the use of muscle relaxants, would be a logical choice. The selection and administration of anesthesia to these patients should be made with the same thoughtfulness and care as for patients with coronary artery disease.

REFERENCES

1. Griffith TW: On myotonia. Quart J Med 5: 229-247, 1912

2. Fearrington EL, Gibson TC, Churchill RE: Vectorcardiographic and electrocardiographic findings in myotonia atrophica. Am Heart J 67:599-609, 1964

3. Payne CA, Greenfield JC: Electrocardiographic abnormalities associated with myotonic dystrophy. Am Heart J 65:436-440, 1963

4. Holt JM, Lambert EHN: Heart disease as the presenting feature in myotonia atrophica. Br Heart J 26:433-436, 1964

5. Fisch C, Evans PV: The heart in dystrophia myotonica: report of an autopsied case. N Engl J Med 251:527-529, 1954

6. Ravin M, Newmark Z, Saviello G: Myotonia dystrophica—an anesthetic hazard: two case reports. Anesth & Analg 54:216-218, 1975

Comment

DEAN H. MORROW, MD
Department of Anesthesiology
Baylor College of Medicine
Texas Medical Center
Houston, Texas

Doctors Meyers and Barash are to be complimented for bringing to our attention this observation of altered intracardiac impulse conduction and associated hemodynamic deterioration while anesthetizing a patient with myotonic dystrophy.

The sequence of electrocardiographic events described in this case history suggests a responsible anesthetic-related electrophysiologic conduction alteration. Two previous reports[1,2] indicate that intracardiac conduction is prolonged by both halothane and methoxyflurane in normal dogs. Unfortunately, similar measurements have not been performed with enflurane in either normal or myogenic animal models. Thus, one can only speculate that in this patient, enflurane suppressed conduction sufficiently to produce right bundle branch block and resultant hemodynamic deterioration. The observation that discontinuation of enflurane and administration of atropine and mephentermine increased heart rate sufficiently to restore adequate cardiac output, and that this favorable chronotropic response occurred despite a temporary persistence of the conduction deficit, should be borne in mind by those faced with a similar situation. In the event of an atropine-resistant bradycardia, IV isoproterenol infusion or transvenous ventricular pacing might be required.

Hopefully, in the near future, comprehensive data will be available defining the effects of all currently used anesthetic combinations on intracardiac conduction. This information should permit improved anesthetic management of patients with heart block of many etiologies and, in particular, that group in which the conduction alteration is a part of the myotonic dystrophy syndrome.

REFERENCES

1. Morrow DH, Haley JV, Logic JR: Anesthesia and digitalis. VII. The effect of pentobarbital, halothane and methoxyflurane on the A-V conduction and inotropic responses to ouabain. Anesth & Analg 51:430-438, 1972

2. Atlee JL III, Rusy BF: Halothane depression of A-V conduction studied by electrograms of the bundle of His in dogs. Anesthesiology 36:112-118, 1972

Comment

MARTIN D. SOKOLL, MD
Department of Anesthesia
University of Iowa Hospitals
Iowa City, Iowa

Myotonic dystrophy is usually thought to be a disease affecting principally skeletal muscle. There is, however, increasing evidence of cardiac involvement in most, if not all, patients with this disease.[1] Patients with this dystrophy often die suddenly. Caughey and Myrianthopoulos[2] attribute this to the sudden development of lethal arrhythmias. Likewise, these patients are known to develop sudden bouts of congestive failure without other predisposing cause.[1,2]

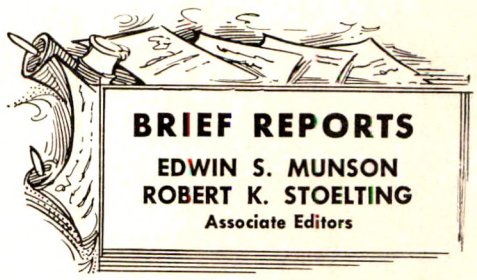
On the standard ECG, the commonest abnormality noted in patients with myotonic dystrophy is some type of conduction defect. This abnormality is seen in at least 50% of such patients. Griggs' group[3] inserted both His-bundle recording electrodes and atrial-pacing electrodes in 11 patients with this disease. Three patients had normal ECGs, while the remaining 8 had obvious conduction defects. All 11 patients developed Wenckebach phenomenon at rates of 140 bpm or less. This is considered an abnormally slow rate for the appearance of conduction defects. These data strongly suggest that all patients with myotonia dystrophica have either overt or latent conduction abnormalities.

REFERENCES

1. Zellweger H, Ionasescu V: Myotonic dystrophy and its differential diagnosis. Acta Neurol Scand 49 (Suppl 55):1-28, 1973

2. Caughey JE, Myrianthopoulos NC: Dystrophia Myotonia and Related Disorders. Springfield, Illinois, Charles C Thomas, Publisher, 1963, p 35

3. Griggs RC, Davis RJ, Anderson DC, et al: Cardiac conduction in myotonic dystrophy. Am J Med 59:37-42, 1975



Defective Disposable Endotracheal Tube

TAI-MAO CHIU, MD*
ELSIE F. MEYERS, MD†
St. Louis, Missouri‡

IN THE past few years, sterile disposable polyvinyl-chloride endotracheal tubes have been widely utilized with a good safety record. Complications have included damage to tissues caused by polymers and elastomers, problems with the cuffs, and defective material within the lumen.[1-4]

We recently encountered a new hazard: the punched-out area forming the Murphy eye was still in situ (figure). This irregularity was noted prior to intubation. On application of pressure, the punched-out piece came loose and fell into the lumen of the tube. Vigorous tapping was required for dislodgement.

This report is a reminder of the importance of careful inspection of endotracheal tubes in order to avoid introduction of an endotracheobronchial foreign body.

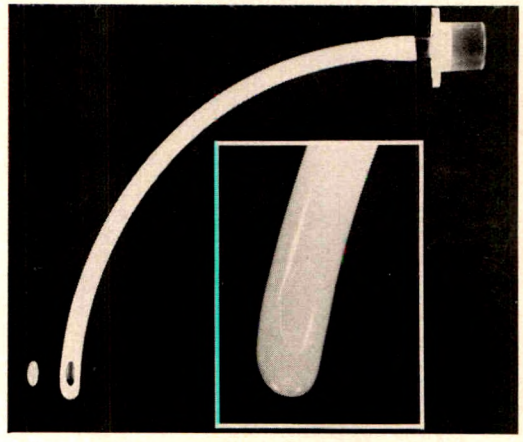


FIGURE. The punched-out area forming the Murphy eye: a possible foreign-body hazard.

REFERENCES

1. Blanc VF, Tremblay NAG: The complications of tracheal intubation: a new classification with a review of the literature. Anesth & Analg 53:202-213, 1974

2. Ketover AK, Feingold A: Collapse of a disposable endotracheal tube by its high-pressure cuff. Anesthesiology 43:108-110, 1975

3. Stetson JB, Guess WL: Causes of damage to tissues by polymers and elastomers used in the fabrication of tracheal devices. Anesthesiology 33: 635-652, 1970

4. Stobor D: Danger of aspiration due to defective material of endotracheal tubes. Zentralbl Chir 99: 698-699, 1974

*Resident.

†Assistant Professor.

‡Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri 63110.

Paper received: 10/16/75
Accepted for publication: 11/16/75

Fatal Complication from Swallowed Denture Following Prolonged Endotracheal Intubation: A Case Report

GUNNAR A. KROESEN, MD*
BRUNO C. HAID, MD†
Innsbruck, Austria‡

A 49-YEAR-OLD woman was involved in a traffic accident and suffered shock, cerebral concussion, bilateral maxillary fractures, basal skull fracture, and multiple lacerations of the legs. During the first 2 weeks of her hospitalization, the patient remained intubated with a #8 disposable polyethylene cuffed orotracheal tube. The cuff was only intermittently inflated. The patient was extubated on the 13th day.

Immediately after extubation, she developed mild laryngeal stridor, which responded well to cortisone and calcium therapy. Within 3 hours, the patient was breathing easily and spontaneously, although she was still unable to speak.

Five hours later, while her nurse was performing oral toilet, the patient became cyanotic and then suffered a complete respiratory arrest. Artificial respiration was administered with a bag and mask, but the patient's thorax did not move. About 3 minutes later, reintubation was attempted 3 times without success. The glottis, which could be visualized, was bluish and swollen. Cardiac arrest occurred and external massage was started immediately. An emergency tracheotomy was performed.[1] Ventilation was begun and the standard cardiopulmonary resuscitation measures were applied, but without success.

A postmortem direct laryngoscopy revealed a fragment of the patient's dentures hooked and firmly lodged in the larynx beyond the vocal cords (figure). Apparently, it had been lying somewhere in the pharynx since the day of accident and (after over 13 days of tracheal intubation and more than 5 hours following extubation) was aspirated

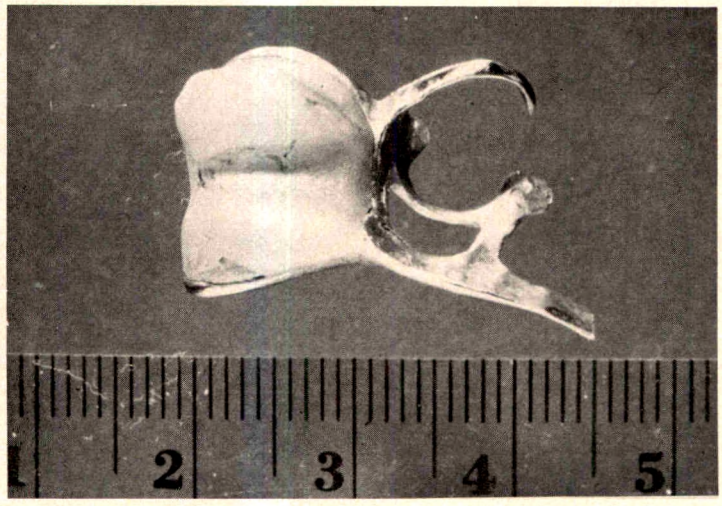


FIGURE. Fragment of broken dentures, easily removed from larynx by forceps at necropsy.

*Assistant Professor.
†Professor.
‡Department of Anesthesiology and Reanimation, Medical School, University Hospitals, Innsbruck, Austria.

Paper received: 8/20/75
Accepted for publication: 10/31/75

during the last oral toilet, blocking the upper airway completely.[2] However, it was removed with a Magill forceps.

This case report emphasizes the importance of carefully examining dentures for evidence of fragments that may be left behind in the upper airway.

REFERENCES

1. Kroesen G, Leitner E: Tracheotomie in der Intensiv-Therapie. Z Allgemeinmed 6:285-288, 1974

2. Blanc VF, Tremblay NAG: The complications of tracheal intubation: a new classification with a review of the literature. Anesth & Analg 53:202-213, 1974

Hypercapnia During Cyclopropane Anesthesia: A Case Report

STEPHEN T. BARASCH, MD*
SANDRA BOOTH, CRNA†
JEROME H. MODELL, MD‡
Gainesville, Florida§

CYCLOPROPANE usually is administered by a closed-circle system which relies entirely on chemical CO_2 absorption to avoid hypercapnia. A properly functioning anesthesia machine and breathing circle are essential with this anesthetic technic. A case report of hypercapnia caused by defective equipment during closed-circle cyclopropane anesthesia is described and methods of avoiding this complication are suggested.

A healthy 21-year-old woman scheduled for vaginal hysterectomy was premedicated with pentobarbital (100 mg), meperidine (25 mg), and atropine (0.4 mg) IM. After 45 minutes, anesthesia was induced with thiopental (50 mg) IV and 50% cyclopropane in O_2, administered by face mask via a closed-circle absorber system (total flow 0.5 L/min). The concentration of cyclopropane gradually was reduced to 15%. Approximately 10 minutes after induction, multifocal ventricular premature contractions were noted. Lidocaine (50 mg) was given IV with no apparent effect. About 5 minutes later, the patient appeared to be hyperventilating, with very deep respirations. Her pupils were dilated and skin appeared mottled. Blood drawn from the radial artery showed a pH of 7, $Paco_2$ of 108 torr, and Pao_2 of 320 torr.

Cyclopropane was discontinued and N_2O-O_2 (3:2 L/min) was passed into the circle system. The patient's color improved and her respirations became less labored. Blood drawn 15 minutes later showed a pH of 7.34, $Paco_2$ of 37 torr, and Pao_2 of 230 torr. Ventricular arrhythmias ceased shortly after increasing the fresh gas flow rate to the circle system, and the surgical procedure was completed without further incident. The patient's systolic blood pressure ranged from 110 to 130 torr and her pulse from 90 to 110/min throughout the procedure. She was taken to the recovery room in good condition and had an uneventful postoperative course. The anesthesia machine was removed from the operating room and tested.

Equipment Test.—To assess the efficacy with which the circle system absorbed CO_2, we evaluated ventilatory responses of a volunteer subject. A Godart capnograph was placed just distal to the inspiratory valve and a pneumotachygraph was connected in series with the expiratory hose at the mask Y connector. The expiratory flow was analyzed electronically on a Model M300 Respiratory Parameter Monitor,* to give instantaneous values for minute volume ($\dot{V}_E$), respiratory rate in breaths per minute (f),

*Systems Research Laboratories, Inc, Dayton, Ohio.

*Chief Resident, Critical Care.

†Nurse Anesthetist.

‡Professor and Chairperson.

§Department of Anesthesiology, University of Florida College of Medicine, J. Hillis Miller Health Center, Gainesville, Florida 32610.

Paper received: 9/30/75
Accepted for publication: 11/6/75

TABLE

Ventilatory Responses in a Volunteer Breathing O_2 in a Closed-Circle System for 15 Minutes Followed by O_2 in a Semiclosed-Circle System (5 L/min) for 15 Minutes

	Closed system				Semiclosed system		
	Start	5 min	10 min	15 min	20 min	25 min	30 min
$\dot{V}_E$, L/min	5.2	8.7	10.9	16.1	10.9	8.5	7.6
Vt, L	0.29	0.45	0.48	0.62	0.53	0.49	0.43
f	18	19	23	26	20	17	17
F_{ICO_2}	0	0.05	0.06	0.08	0.05	0.04	0.03

and tidal volume (Vt). The capnograph permitted continuous monitoring of the CO_2 concentration of inspired gas (F_{ICO_2}).

The soda lime was confirmed to be white and the canister bypass valve of the Ohio Model 21 absorber† to be closed fully. We administered O_2 by face mask via the closed system, continuously recording $\dot{V}_E$, Vt, f, and F_{ICO_2}. After 15 minutes, the breathing circle was changed to a semiclosed system by opening the pop-off valve and increasing the O_2 flow rate to 5 L/min. The test was continued for an additional 15 minutes. Results are shown in the table.

Since the failure of the anesthesia machine to absorb CO_2 had been confirmed, we dismantled the breathing-circle components to search for the cause. The canister bypass valve was closed and functional and inspiratory and expiratory valves were in good working order. The soda-lime granules were white, cool, and adherent, forming a solid cake.

Granules from the cake, tested on a blood-gas machine for CO_2 absorbing capacity by placing them in a column through which was flowed a mixture of 10% CO_2 and 90% N_2, gave a P_{CO_2} of 72 torr inflowing and 68 torr effluent, indicating almost no CO_2 absorption. The granules remained white and cool during the 12-minute test period. As a control, fresh indicator soda lime, tested in an identical manner, showed an inflow P_{CO_2} of 72 torr and an effluent P_{CO_2} of less than 10 torr (the lower limit of the blood-gas machine). These granules turned blue within 2 minutes and the column felt warm. Water condensed on the column wall. An additional sample of granules from the absorber was analyzed by a manufacturer‡ of indicator-grade soda lime and was found to have "no indicating qualities."

†Ohio Medical Products, Madison, Wisconsin.

‡W. A. Hammond Drierite Company, Xenia, Ohio.

DISCUSSION

Our practice has been to replace the upper CO_2 absorption canister with the lower canister when the upper attains a stable blue color, and to place fresh soda lime in the lower section. In proposing the use of the double canister, Elam[1] stated that "cycling of the two chambers of absorbent insures complete removal of carbon dioxide . . ." and suggested that the chambers be cycled after 8 hours of rebreathing in a closed-circle system. However, since significant CO_2 leakage through the canister can occur in 5.5 hours if the absorbent is packed incorrectly and peripheral channeling results,[2] time of use *per se* is an unreliable indicator of CO_2 removal.

While recognizing the value of indicator dye in the double canister system, Adriani[3] stressed that measuring the CO_2 concentration of gas after canister use is the only reliable method to judge the completeness of CO_2 absorption.

We have shown that the complete absence of blue color in soda lime assumed to contain ethyl-violet indicator does not insure that the soda lime is capable of CO_2 absorption. Furthermore, since soda lime is manufactured both with and without indicator, it is possible that soda lime without indicator may inadvertently be used. Nevertheless, we were able to detect soda-lime exhaustion by analysis of CO_2 concentration of gas within the inspiratory hose of the circle system.

We do not know when the soda lime was last changed in our machine; however, other patients were anesthetized previously without apparent difficulty. In those patients, however, a semiclosed technic with 5 L/min flows was used; thus, there was little dependence on the absorption canister for CO_2 removal.[4] It was not until we used a closed-circle system (0.5 L/min inflow rate) that the problem was apparent.

In the clinical situation in which incomplete CO_2 absorption is suspected, it is a simple procedure to withdraw a sample of gas from the inspiratory hose and determine the P_{CO_2} with either a CO_2 electrode or an infrared CO_2 analyzer. This maneuver would have been helpful in detecting our problem earlier.

ACKNOWLEDGMENT

The authors thank Don Carlson for his technical assistance.

REFERENCES

1. Elam JO: The design of circle absorbers. Anesthesiology 19:99-100, 1958

2. Hampton LJ: Absorption of carbon dioxide: influence of canister design on performance characteristics of commercial absorbers. Anesthesiology 28:255-256, 1967

3. Adriani J: Disposal of carbon dioxide from devices used for inhalational anesthesia. Anesthesiology 21:742-758, 1960

4. Benson DW, Graff TD, Hurt HH, et al: The circle semi-closed system control of $P_{A_{CO_2}}$ by inflow rates of anesthesia gases and hyperventilation (abstract). Anesthesiology 29:174, 1968

Calibration of the Narkotest® Gas Monitor for Isoflurane

JOSE L. VELAZQUEZ, MD*
ALFRED FEINGOLD, MS, MD†
Miami, Florida‡

THE Narkotest®§ anesthetic gas analyzer was introduced as a simple, inexpensive device to measure in-circuit halothane concentration.[1] It was later shown to respond to all inhalation anesthetics approximately in proportion to the minimum alveolar concentration (MAC).[2] It consists of 4 strips of silicon rubber connected by a lever to a scale pointer. When exposed to anesthetic agents, the strips relax, causing movement of the pointer. This instrument was shown by Lowe and Hagler[2] to respond linearly to 6 inhalation anesthetics.

We have calibrated the Narkotest for the new anesthetic, isoflurane, and summarized the calibration factors for 9 other anesthetics.

Using an O_2 flow of 5 L/min, selected concentrations of isoflurane up to 3% were equilibrated with the Narkotest monitor. Gas concentrations were measured by a Hewlett-Packard gas chromatograph, using appropriate standards, and were plotted against the reading on the Narkotest. The least squares method was used to determine the best fit line through these points.

The Narkotest response to isoflurane is rectilinear ($r=0.99$). As the slope of the line (calibration factor) is 1.8, the Narkotest reading should be multiplied by 1.8 to obtain the isoflurane concentration in volumes percent. The calibration factors for other anesthetics are summarized in the table (third column).

This calibration factor is proportional to anesthetic rubber/gas and oil/gas solubility and inversely proportional to silicon-rubber retention times.[2] Therefore, more potent anesthetics require lower gas concentration to cause the same deflection of the pointer. Since anesthetic potency is correlated with oil/gas solubility, the Narkotest monitor roughly approximates the "MAC meter" suggested by Lowe.[2] When the Narkotest

§North American Drager, Telford, Pennsylvania.

*Research Trainee.

†Assistant Professor.

‡Department of Anesthesiology, University of Miami School of Medicine and Veterans Administration Hospital, Miami, Florida 33152.

This study was supported in part by NIH Grant #5 Tol GMO 1714-09.

Reprint requests to Dr. Feingold.

Paper received: 6/23/75
Accepted for publication: 8/21/75

TABLE

Narkotest Anesthetic Gas Monitor Calibration Factors and Reading at 1 MAC for 10 Anesthetic Agents*

Anesthetic	MAC[4] (volumes %)	Calibration factors for converting Narkotest reading to volumes %	Narkotest reading at 1 MAC
Cyclopropane	9.2	13.0* - 13.5†	0.7*†
Diethyl ether	1.9	1.25* - 1.15†	1.5* - 1.6†
Divinyl ether	3.0	2.3†	1.3†
Enflurane	1.7	1.46* - 1.64†	1.2* - 1.0†
Fluroxene	3.4	2.3*	1.5*
Halothane	0.75	1.0*†	0.8*†
Isoflurane	1.3	1.8‡	0.7‡
Nitrous oxide	101.0	151.0‡ - 171.0†	0.7‡ - 0.6†
Methoxyflurane	0.16	0.16* - 0.20†	1.0* - 0.8†
Trichloroethylene	0.2	0.33†	0.6†

*Data from Lowe[2]; †data from White and Wardley-Smith,[3] recalculated for MAC as recommended by Steward and associates.[4]

‡Authors' data.

readings at 1 MAC are calculated (last column, table), the readings range from 0.6 for trichloroethylene to 1.6 for diethyl ether.

REFERENCES

1. Scurr C, Feldman S: Scientific Foundations of Anesthesia. Philadelphia, FA Davis Company, 1970, pp 56-57

2. Lowe H, Hagler K: Clinical and laboratory evaluation of an expired gas monitor (Narko-test). Anesthesiology 34:378-382, 1971

3. White DC, Wardley-Smith B: The "Narkotest" anaesthetic gas meter. Br J Anaesth 44:1100-1104, 1972

4. Steward A, Allott PR, Cowles AL, et al: Solubility coefficients for inhaled anaesthetics for water, oil, and biological media. Br J Anaesth 45:282-293, 1973

We Salute . . .

Paul Rudolph Dumke, M.D.

OUR nominee for this traditional "Salute" offers a synthesis of the better attributes of the many thus honored over the years. A portrait of Paul Rudolph Dumke imparts the characteristics of a proud Prussian-Germanic heritage and the area of our country in which he was reared—that romantic and culturally rich region known as The Western Reserve—carved out of the old Northwest Territory. Born in 1911, the only child of Richard Rudolph and Martha Schmidt, young Paul had a strict Lutheran upbringing, progressing through the public school system, where his versatility in learning, leadership, and athletics was ever apparent.

Matriculation at Oberlin on a merit scholarship witnessed the beginning of a series of encounters with wise preceptors who would leave a lasting impress on the student's mind. One would have had Paul concentrate on Germanic studies, another offered the lure of chemistry.

And so it came to pass in 1937, at Western Reserve University Medical School, where certain workers in the vineyard of hypertension, such as Harry Goldblatt and Joseph Hayman, were attracted by the qualities of their student, Dumke. Through their guidance, his path led to the University of Pennsylvania, to the Departments of Pharmacology and Physiology and the inspiration of the inventive minds of Carl R. Schmidt, Grayson McCouch, and Julius H. Comroe, Jr. More than a few publications on respiration and circulation bear the name of Dumke et al.

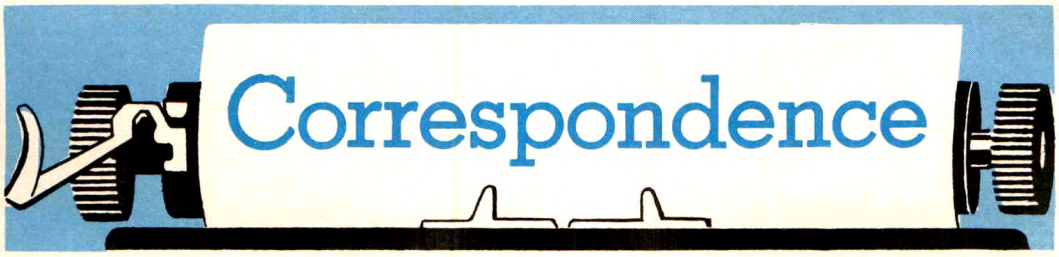
But, time out in 1937 for a felicitous union with Dorothy Louise Foster, and subsequent issue: Robert, now a teacher in the Detroit school system; and Catherine, a paralegal assistant in a Detroit firm. Early on, the family moved from town to town in line of military duty. Those who know the man would not be surprised to learn that medical soldier Dumke terminated a career in the Reserves with the rank of Lieutenant Colonel. Likewise, how logical it was that he should soon join the burgeoning army of anesthetists.

At the University of Pennsylvania in the "forties and fifties." Dr. Dumke earned a reputation as superb clinician, pacifier of surgeons such as I. S. Ravdin, and stern but

sympathetic teacher of beginners. As it is the mission of an academic department to disseminate wisdom, Paul Dumke, by now a professor, was the first to desert the ranks of Dripps, Lamont, Eckenhoff, and Vandam, for the post of Chief at the Henry Ford Hospital in Detroit, in 1953. While building an exemplary program there, time was sequestered for organizational work: Director of the ASA; Governor of the College; Chairman of the AMA Section on Anesthesiology; and Trustee of the IARS.

You would have to say of Paul Dumke's other pursuits that in general he relishes every facet of living: gourmanderie, quaffing, the aroma of fine tobacco, piscation, gunning, bidding the grand slam, and savouring the printed word. On principle, he religiously shuns exercise but keeps a poodle on leash. A recent tribute by cohorts of the IARS depicts Paul Dumke as a dear and true industrious friend—strong, constant, pleasant, and wise!

NITROUS OXIDE AND CARDIAC PAIN. A double blind study in 69 patients with chest pain following acute myocardial infarction compared 35% nitrous oxygen with 100% oxygen as an analgesic. Both drugs were inhaled for 5 minutes. Nitrous oxide had a beneficial effect in 74% of the episodes of pain and produced complete pain relief in 39%. In contrast, oxygen produced partial relief in 29% and complete relief in none. Blood pressure and heart rate did not change significantly during nitrous oxide inhalation. There was no evidence of bone marrow depression in 3 patients who had inhalations lasting a week. Nitrous oxide offers an alternative to narcotics for mild cardiac pain and a useful adjunct to narcotics for severe pain. *(Thompson PL, Lown B: Nitrous oxide as an analgesic in acute myocardial infarction. JAMA 235: 924-927, 1976)*



To the Editor:

The effects of ketamine (Ketalar®, Ketaject®) on the EEG in normal adult subjects and in epileptic patients are controversial. Some authors[1] have found no evidence that ketamine induces seizure discharges in epileptics or normals, while others[2-4] warn of the drug's potential epileptogenicity. We recently completed a study[5] on this subject that may be of interest to anesthesiologists.

In our study of ketamine in 26 patients (16 men, 10 women, ages 17 to 58 [mean 31.3 years]) with an unequivocal history of either focal or generalized epilepsy, the effects of ketamine (1.5 to 2 mg/kg) were measured with serial EEGs for each patient while awake with hyperventilation and photic stimulation, while asleep after 18 to 24 hours of sleep deprivation, and during and after IV injection of ketamine.

After administration of ketamine, all patients developed a catatonic state, which was dose related in duration. Twenty-two patients hypoventilated and/or had respiratory dysrhythmia with brief episodes of apnea; 5 had longer episodes of apnea requiring brief supportive ventilation.

Characteristic EEG changes appearing during ketamine anesthesia consisted of generalized high-amplitude synchronous beta waves, often in association with generalized theta waves of 4 to 5 cps. Quasiperiodic delta complexes every 2 to 6 seconds, having amplitudes of up to 400 microvolts, were seen in 9 patients.

Several behavior changes apparently induced by ketamine were observed. Unusual postures were exhibited by 12 subjects, distorted perceptions by 25, motor hyperactivity by 5, and sporadic myoclonic jerks by 1 patient suffering from psychomotor seizures. No patients developed seizures. There was a striking dissociation between EEG changes and behavior. The same EEG features of theta and synchronous beta activity were seen during the catatonic and recovery stages. Furthermore, no behavior differences could be noted between periods with quasiperiodic delta and periods with generalized theta activity.

To be sure that EEG and behavior changes under ketamine anesthesia were not just coincidental, we compared them with observations made during physiologic awake and asleep states, using the following criteria: Type 1 activation was defined as the occurrence of epileptic discharges (ED) in the tracing following the testing procedure when no such abnormality was present in the awake tracing. Type 2 activation was defined as an increase of 30% or more in the frequency of ED following the activating procedure when such discharges were already present in the awake record. ED was defined as spikes and/or spike and wave complexes, either focal or generalized.

Nine patients had normal awake tracings; in 2, type-1 activation occurred both during sleep and during ketamine anesthesia. Seventeen patients exhibited type-2 activation, 12 during sleep and 6 during ketamine anesthesia. In 15 patients, ED was either precipitated or aggravated by spontaneous sleep, while ED followed ketamine anesthesia in 8 awake patients. Ketamine appeared less apt to activate temporal-lobe ED than generalized ED. Two of the 12 patients with temporal-lobe seizures had a decrease or complete suppression of ED during ketamine anesthesia. In this study ketamine did not display epileptogenic activity.

Our findings[5] are certainly consistent with those of Corssen's group[1] and contradict those reported by Ferrer-Allado[2] and by Bennett and associates[3] and the implications of Winters,[4] all of whom suggest that ketamine may precipitate or aggravate seizures in the epileptic patient. One point might be re-emphasized, namely, that when epileptic patients are studied, any seizures that occur in the experimental condition may be coincidental. In our study, we compared EEG activity in these patients both under ketamine anesthesia and under normal waking and sleep-deprived sleeping states. Under these controlled conditions, we found that, with ketamine, abnormal EEG activity or aggravation was certainly no more common than under the other conditions and perhaps even less so.

Gastone G. Celesia, MD
Betty J. Bamforth, MD
Rong-Chi Chen, MD
Departments of Neurology and Anesthesiology
University of Wisconsin Center for Health Sciences
Madison, Wisconsin

REFERENCES

1. Corssen G, Little SC, Tavakoli M: Ketamine and epilepsy. Anesth & Analg 53:319-335, 1974

2. Ferrer-Allado T, Brechner VL, Dymond A, et al: Ketamine-induced electroconvulsive phenomena in the human limbic and thalamic regions. Anesthesiology 38:333-344, 1973

3. Bennett DR, Madsen JA, Jordan WS, et al: Ketamine anesthesia in brain-damaged epileptics. Electroencephalographic and clinical observations. Neurology 23:449-460, 1973

4. Winters W: Epilepsy or anesthesia with ketamine. Anesthesiology 36:309-312, 1972

5. Celesia GG, Chen R, Bamforth BJ: Effects of ketamine in epilepsy. Neurology 25:169-172, 1975

* * * * *

To the Editor:

Thank you for giving me an opportunity to answer Dr. Celesia's letter regarding the use of ketamine for epileptic patients. The uniqueness of ketamine's CNS action has led to enormous controversy, opinions ranging from its being the anesthetic of choice[1] to being totally contraindicated[2] in patients with seizure disorders. These controversies result from differences in parameters investigated, differences in experimental models, and differences in EEG interpretation.

Although measuring activation or depression of the CNS by measuring neuronal activity of the brain cells in various parts of the brain is impossible in humans, neuronal activity by measurement of multiple unit activity (MUA) has been measured in animals[3] and in the thalamic area of man[4] before and after administration of anesthetic agents. Winters and associates[3] have reported that, in animals, the MUA in the reticular activating system may be stimulated, with the behavioral appearance of sleep, when EEG waves are similar to those in a state of alertness (low-amplitude fast waves). An example of this is during REM or paradoxical sleep. Dr. Winters also reported that MUA or neuronal activity is stimulated during occurrence of epileptiform discharges in limbic and thalamic regions, while the animal appeared immobile or catatonic after ketamine administration. Therefore, to say whether an anesthetic agent would depress seizure discharges, depression of neuronal activity should be correlated simultaneously with behavior and EEG.

Dr. Celesia studied the cortical EEG in epileptic patients. In our study,[5] we measured, in addition to the cortical EEG, limbic and thalamic EEGs. This did not necessarily correlate with cortical EEG changes. Only when the epileptiform discharges spread to the cortical region did the patient manifest seizure activity. While limbic and thalamic seizure discharges were occurring, patients manifested similar behavior to that reported by Dr. Celesia, such as motor hyperactivity sporadic myoclonic jerks, and unusual postures.

However, the difference between Dr. Celesia's study and ours was in the concomitant measurement of limbic and thalamic EEG, which demonstrated electrical seizure activity during these behavioral manifestations despite a nonsignificant cortical EEG. It is possible

that Dr. Celesia's patients were indeed having limbic and thalamic seizures but that this was not evident on the cortical EEG being measured.

We have also found that the origin of seizure discharge did not necessarily start from the established seizure foci of the individual patient, which means that the existence of seizure foci is not necessary for ketamine to induce seizure discharges. This could explain the isolated reports of normal, seizure-free, patients having seizures after ketamine administration.[6]

In our initial work in unrestricted animals,[3] which had cortical depth EEG electrodes and MUA measurement in the reticular activating system, we found that the MUA following ketamine was higher than control awake, sleep, and REM or paradoxical levels, which further substantiates that ketamine is not a depressant but a stimulant of the CNS.

In Dr. Celesia's initial experiment in animals,[7] although cortical and depth EEG was measured, MUA was not, yet the EEG changes he saw were similar to those in our study. The animals in Dr. Celesia's study were restricted and also given other drugs such as ether, gallamine, and local anesthetics. In our study, the animals were unrestricted and measurements were continuous for several days before ketamine administration, and MUA was measured continuously for 24 to 48 hours up to 7 days after ketamine. No other drugs were given concomitantly.

If ketamine suppresses epileptic discharges, one has to show that ketamine depresses MUA, which is usually increased during a seizure, and not rely only on behavior and the EEG. Dr. Celesia did not measure neuronal activity in both animals and man, mainly relying on behavior and cortical EEG, which does not necessarily correlate with neuronal activity of depth electrode EEG. To convince one that ketamine is indicated for epileptic patients, ketamine should be shown, by MUA measurement, to depress neuronal activity and that correlative existing seizure activity is terminated by ketamine. The ideal study would be to observe the effect of ketamine on neuronal activity in the human brain. Although we have studied such activity in the thalamic area in man with N_2O and thiopental, we are yet to study ketamine. However, our initial results with N_2O and thiopental correlate with those of Dr. Winters.

Theresa Ferrer-Brechner, MD
Department of Anesthesiology
University of California School of Medicine
Los Angeles, California

REFERENCES

1. Corssen G, Little SC, Tavakoli M: Ketamine and epilepsy. Anesth & Analg 53:319-335, 1974

2. Winters W: Epilepsy or anesthesia with ketamine. Anesthesiology 36:309-312, 1972

3. Winters W, Ferrer-Allado T, Guzman-Flores C, et al: The cataleptic state induced by ketamine: a review of the neuropharmacology of anesthesia. Neuropharmacology 11:303-315, 1972

4. Babb T, Ferrer-Brechner T, Brechner V: Limbic neuron firing rates in man during administration of nitrous oxide-oxygen or sodium thiopental. Anesthesiology 43:329-336, 1975

5. Ferrer-Allado T, Brechner VL, Dymond A, et al: Ketamine-induced electroconvulsive phenomena in the human limbic and thalamic regions. Anesthesiology 38:333-344, 1973

6. Thompson GE: Ketamine-induced convulsions. Anesthesiology 37:662-663, 1972

7. Celesia GG, Chen R, Bamfort BJ: Effects of ketamine in epilepsy. Neurology 25:169-172, 1975

* * * * *

To the Editor:

Thank you for the opportunity to comment on the use of ketamine in epileptic patients. Proposals that there is no relationship between EEG burst discharge activity and ketamine may be doing a disservice to patients with abnormal EEGs.

Our published EEG study[1] did not give some of the primary clinical data one needs for a discussion of clinical relevance. Many authors have reported high-voltage delta-wave activity[2] after onset of the low-voltage, rapid-frequency theta-wave discharge. We also illustrated focal spike and wave discharges; these were not "coincidental." Indeed, we used care to eliminate coincidence as much as possible.

We studied our patients over a 3-year period in a special seizure-observation unit. A careful record was kept of seizure frequency and type for 3 months prior to entry in the study. Blood levels of seizure-control medications were taken periodically to assure that absorption was constant and predictable. EEG studies, repeated twice, included sleep and photic stimulation, using the 12 to 20 International System with 17 scalp silver-silver chloride and 2 ear leads. The EMG was also recorded.

For the test period, we did split-image videotape recording to get real-time correlation between motor activity and EEG electrical activity. Since our initially reported study, we have repeated the same study in the experimental group with thiopental and halothane. We have also set up an experimental lesion in the rhesus monkey using a penicillin-induced focal cortical lesion. Thus we carefully excluded coincidental seizure activity and demonstrated a significantly different response of ketamine in comparison with other anesthetic agents. Twenty minutes of continuous baseline tracings certainly gave us ample background data. I should point out, however, that our patients were all children, including two without a seizure history, studied because their "random movements" clinically resembled major motor seizures.

Abnormal EEG rhythms were induced in all patients by ketamine. Motor manifestations were variable, extending from rigidity, predominantly unilateral and periodic, to unilateral clonic-tonic adversive seizures. Tonic-clonic activity was also seen in the two "normal" children, as were polyspike and wave discharges. In the epileptic patients, the EEGs differed from their usual pattern, frequently demonstrating suppression of their usual focus, with subsequent appearance of a mirror-image type focus in the opposite hemisphere. Studies in monkeys uniformally demonstrated this mirror-focus activity on implanted electrodes, as well as burst discharge in subcortical areas which did not always transmit to the cortical electrodes.

The time between administration and onset of seizure activity was variable, IM administration having a more delayed onset. In 1 patient, only IV administration elicited the EEG abnormality. We assume this relates to uptake but did not do blood levels. Onset with the IV route was usually 60 seconds. The duration of change was also variable, 1 patient showing a post-test change in need for antiepileptic drugs. In a second series of 10 patients studied after the initial group, seizure was frequently greater in the recovery period.

Thiopental and halothane studies gave entirely different results, motor activity being suppressed in all. Several had activation of their primary focus by thiopental but no change in electrical activity. Halothane at MAC 1 concentration suppressed the abnormal electrical activity, with reappearance in the recovery period. Thiopental dosage was that necessary to suppress the lid reflex.

It was the conclusion of the pediatric neurologist and the electroencephalographer that there was definitely a relationship between ketamine and epileptiform seizure pattern occurrence. We have now extended the study to a larger group.

If we believe that seizure activation is undesirable in epileptic children, we are led to the conclusion that ketamine is not the ideal anesthetic for such patients. We are aware that the drug is used frequently in neurophysiologic studies. Prior reports[3] of this use, interestingly, include a much higher incidence of rigidity, posturing, excessive secretions, and airway problems. We would wonder what EEG monitoring would demonstrate in these patients.

As for coincidence, these studies were carefully supervised and monitored by our Department of Neurology, and the electroencephalogist reviewed the tracings later off line to rule out bias. The right temporal spike and wave discharges illustrated in one case

occurred after 2 separate injections, once 17½ minutes later and once 21½ minutes later. This patient's baseline EEGs had never before demonstrated right temporal spike and wave discharges. Coincidence? I think not.

William S. Jordan, MD
Department of Anesthesia
The University of Utah Medical Center
Salt Lake City, Utah

* * * * *

To the Editor:

My first impulse after receiving your request for an answer to Dr. Celesia's letter was to pass this round, having previously presented an editorial[1] and a discussion[2] on this topic. However, since the controversy regarding the relationship of ketamine to epilepsy seems endless, I decided to make one more attempt at stating my views. In reviewing the controversial reports pro[3-10] and con,[11-13] several pertinent points appear to be confused.

1. Epilepsy is not one state but a series of syndromes encompassing:
   a. Abnormal EEG activity, or
   b. Abnormal EEG activity associated with some motor response, such as ear twitching, or
   c. "b" plus gross motor and electrical discharges.

2. The EEG patterns induced by ketamine in animals and man are—in my opinion—epileptogenic; that is, the midbrain, diencephalic, and cortical hypersynchronous 1 to 4 Hz EEG slow waves of high amplitude, alone or intermixed with spike bursts, represent epileptic brain-wave activity.[3,7] Even the EEG patterns which we describe during stages II-A and II-B anesthesia are epileptogenic.[7] The intermittent appearance of high-amplitude, high-frequency seizure discharges in the limbic lobe during ketamine-induced cataleptic anesthesia (stage II-C) is sometimes associated with facial or hind-limb twitching.[3,7] Limbic seizures of this type are often reported to be characterized by bizarre, inappropriate, and cataleptoid behavior in man.

3. Grand mal seizures were not often noted following high doses of ketamine. However, the parent agent, phencyclidine, induces a similar progression of actions. During phencyclidine-induced cataleptic anesthesia, limbic seizures with hind-limb twitches were also noted.[10] Doses of phencyclidine slightly higher than those necessary to induce cataleptic anesthesia induce the same progression, followed by generalized grand mal seizures (fig 11).[10]

4. Epileptics manifest a variety of subcategories of signs, symptoms, and etiologies. The fact that some investigators demonstrated that ketamine increased epileptic activity,[1-10] and others an inhibition,[11-13] implies variations in experimental design, such as varying degrees of antiepileptic pretreatment or a variance in the subcategory of the epilepsy studied. Thus, epilepsy can not be discussed in simplistic terms. Diphenylhydantoin is not effective against all forms of epilepsy. Even patients who respond to this agent may exacerbate the epileptic syndrome following significant elevation of the dosage. Some epileptics have asymptomatic periods. In addition, antiepileptic agents appear to be more effective at some periods than at others. Thus epilepsy is time, drug,

and dose dependent. Ketamine may improve some epileptics, make some worse, and have no effect on others.

5. Dr. Celesia claims to have observed a striking dissociation between EEG and behavior. He warns against excessive or exclusive reliance on the EEG to understand the nature of ketamine anesthesia. He offers no better criterion and leaves us with a sense of a "supernatural" action of ketamine. Most paradoxical situations in neuropharmacology in which behavior and EEG do not seem to be clear-cut eventually resolve themselves. They are usually an indication of our lack of sufficient knowledge to make the correlation. To imply categorically that there is no correlation between behavior and EEG is absurd.

6. Dr. Celesia[12] further asserts that we[7] write: "The anesthetic state induced by ketamine is due to 'limbic seizures.' " We make no such statement. Where he conjured up this statement is not clear, but what is clear is that he did not read our paper carefully. We state that during cataleptic anesthesia, limbic seizures may occur. In our figure 9, demonstrating the EEG during the catatonic state, the limbic seizure appears at 5 minutes but not at 30 minutes. In our Methods section, we describe the gross behavior, EEG, and multiple unit activities necessary for the cataleptic state of anesthesia; limbic seizures are not mentioned.

7. In the discussion of Dr. Corssen's paper,[11] Dr. Domino states: "It is not good medical practice to slander a drug without thorough proof." We believe that scientific investigations should be designed to elicit the truth regarding the nature of a drug action irrespective of its clinical reputation. It is our hope that Dr. Domino did not really wish his statement to read as it does. As was pointed out by Schettini[2] and my subsequent discussion of his paper, if one is aware of the pharmacologic actions of a drug, it may be combined with appropriate agents to block the potentially dangerous actions and augment the more desirable effects; antiparkinson therapy with phenothiazines is an example of this. Thus, I regard our search for an understanding of the properties of drugs such as ketamine to be necessary for improved patient care.

8. It must be reiterated that, as an anesthesiologist, you must make the final decision on the utility of each agent you use. Please read the pertinent papers regarding this controversy and decide for yourself the place that ketamine and drugs of this type have in your anesthetic routine, especially in the epileptic or neurosurgical patient. By being aware and concerned with anesthetic problems such as these, the body of anesthesia knowledge will widen, anesthesiologists' skills will broaden, and patient care will improve.

W. D. Winters, MD, PhD
Department of Pharmacology
University of California School of Medicine
Davis, California

REFERENCES

1. Winters WD: Epilepsy or anesthesia with ketamine. Anesthesiology 36:309-312, 1972

2. Winters WD: Discussion in: Schettini A, Wilder BJ: Effects of anticonvulsant drugs on enflurane cortical dysrhythmias. Anesth & Analg 53:951-962, 1974

3. Ferrer-Allado T, Brechner VL, Dymond A, et al: Ketamine-induced electroconvulsive phenomena in the human limbic and thalamic regions. Anesthesiology 38:333-344, 1973

4. Bennett DR, Madsen JA, Jordan WS, et al: Ketamine anesthesia in brain-damaged epileptics. Electroencephalographic and clinical observations. Neurology 23:449-460, 1973

5. Mori K, Kawamata M, Mitani H, et al: A neurophysiologic study of ketamine anesthesia in the cat. Anesthesiology 35:373-383, 1971

6. Kayama Y, Iwama K: The EEG evoked potentials and single-unit activity during ketamine anesthesia in cats. Anesthesiology 36:316-328, 1972

7. Winters WD, Ferrer-Allado T, Guzman-Flores C, et al: The cataleptic state induced by ketamine: a review of the neuropharmacology of anesthesia. Neuropharmacology 11:303-315, 1972

8. Manohar S, Maxwell D, Winters WD: Development of EEG seizure activity during and after chronic ketamine administration in the rat. Neuropharmacology 11:819-826, 1972

9. Chen CF, Chow SY: Effects of ketamine on synaptic transmission in cat spinal cord. Neuropharmacology 14:147-149, 1975

10. Winters WD, Mori K, Spooner G, et al: The neurophysiology of anesthesia. Anesthesiology 28: 65-80, 1967

11. Corssen G, Little SC, Tavakoli M: Ketamine and epilepsy. Anesth & Analg 53:319-335, 1974

12. Celesia GG, Chen R, Bamforth BJ: Effects of ketamine in epilepsy. Neurology 25:169-172, 1975

13. Celesia GG, Chen RC: Effects of ketamine on EEG activity in cats and monkeys. Electroencephalogr Clin Neurophysiol 37:345-353, 1974

* * * * *

To the Editor:

Dr. Eli Brown's article on the single-needle lateral approach for lumbar sympathetic block[1] alludes to the lack of previous descriptions of this technic in the literature.

We described this technic in ASA Annual Refresher Courses in 1973, 1974, and 1975, as well as in *Refresher Courses in Anesthesiology,* volume 3, 1975 and *Advances in Neurology,* volume 4, 1974.

The major advantage of the lateral approach at L-2 as described above is the use of smaller quantities of local anesthetic or neurolytic agents. Since the preganglionic outflow from the cord to the sympathetic chain ends at L-2, there is no need to produce block below that level. As the sympathetic chain lies in what is only a potential fascial plane, this plane is distended by the local anesthetic introduced. There is no evidence to indicate that table tilting is necessary to involve adjacent segments. We have demonstrated this fact radiographically in the cervical region in our article on stellate ganglion block.[2]

Using a distance of 10 cm rather than 12½ cm from the midline as the needle point of entrance, we have been able to avoid puncture of the kidney, a complication suggested by Dr. Brown. In a large series of patients, we have had no renal complications. Problems with this technic have been related only to improper needle placement, which are obviated by radiographic control.

Harold Carron, MD
Director, Nerve Block & Pain Studies Clinic
Department of Anesthesiology
University of Virginia Medical Center
Charlottesville, Virginia

REFERENCES

1. Brown EM, Kunjappan V: Single-needle lateral approach for lumbar sympathetic block. Anesth & Analg 54:725-729, 1975

2. Carron H, Litwiller R: Stellate ganglion block. Anesth & Analg 54:567-570, 1975

* * * * *

To the Editor:

I want to thank Dr. Carron for directing me to the sources listed in his Letter to the Editor. Although I was unable to find a description of the technic for a lateral approach to sympathetic block at L-2 in either *Advances in Neurology* or *ASA Refresher Courses in Anesthesiology,* volumes I and II, I did find an excellent description of the procedure used by Dr. Carron in *ASA Refresher Courses in Anesthesiology,* volume III, 1975. Unfortunately, this publication was not available to us until after our article was prepared for publication.

In any event, I do not understand how Dr. Carron can be certain that he does not inadvertently puncture the kidney, particularly in view of the proximity of that organ to the path of his needle, and our experience with cadavers. I honestly do not know whether or not inadvertent puncture of the kidney is harmful, but it seems to me that one should avoid it by performing the block at a lower level. Even though our technic requires

a larger volume of solution, I think Dr. Carron would agree that the use of 20 ml of 1% lidocaine or 0.25% bupivacaine is not excessive.

Eli M. Brown, MD
Department of Anesthesiology
Sinai Hospital of Detroit
Detroit, Michigan

* * * * *

To the Editor:

I would like to make some additional comments regarding the "Single-Needle Lateral Approach for Lumbar Sympathetic Block" by Brown and Kunjappan.

We have used a slightly different technic of lateral approach, also using a single needle for temporary blocks with local anesthetics, and a double-needle technic for permanent sympathectomies using 6% aqueous phenol.

We place the patient in the lateral position with the side to be blocked upward. A 6-inch needle is inserted between the rib cage and iliac crest, about 12 to 13 cm from the posterior midline, and aimed at a 35 to 40 degree angle toward the anterior surface of the vertebral body. After impinging on the vertebral body, the needle is walked off, until it is just anterior to the body, and the medication is injected.

For blocks using local anesthetics, no x-rays are taken. For permanent sympathectomies with 6% aqueous phenol, we have found better results and longer-lasting blocks by using 2 needles through a single skin wheal by the lateral approach. One needle is pointed upward and the 2nd needle downward, so that they impinge on the bodies of L-2 and L-4 or L-3 and L-5. X-rays are always taken (PA and laterals) to confirm their position, and 4 ml of 6% aqueous phenol is injected at each level.

The procedure is not usually painful, except when the needle hits the periosteum of the vertebral bodies. A small amount of local anesthetic usually eliminates this pain.

We have done over 500 phenol sympathectomies, using the described technic, over the past 10 years, with 2 serious complications: retroperitoneal hemorrhages, which required only conservative management. Other, more common complications, have been backache, lasting a few days, and inguinal burning and paresthesias, lasting a few days to a few weeks. The latter occur in about 10 to 15% of the patients.

Since we often do these blocks on very-poor-risk patients, with far-advanced disease, a number of patients have died from their underlying heart disease, or have lost limbs which did not improve with the sympathectomy. In no patient could this be directly related to the sympathetic block.

The so-called "steal syndrome," where deep circulation gets worse at the expense of superficial warming and improved color in the sympathectomized limb, has not happened in our experience.

Bernard Horn, MD
Chief of Anesthesiology
Kaiser Permanente Medical Center
Vallejo, California

* * * * *

To the Editor:

I enjoyed reading Dr. Brown's article, "Single Needle Lateral Approach for Lumbar Sympathetic Block." His method is indeed simpler and more comfortable to the patient than the classic approach. But it is not original. Besides Lewis' sketchy technic mentioned by Dr. Brown, there exist at least 3 lateral, 1-or-2 needle, approaches.[1-3]

Reid and Shumacker point out the advantages cited by Dr. Brown (accuracy, simplicity, comfort to the patient), and the spread of the solution along the whole lumbar sympathetic chain. Reid places 2 needles 10 to 12 cm laterally to the spines of L-3 and L-4 and directs them to clear the anterolateral border of the vertebral bodies. Even only 6 ml of phenol suffice to block the lumbar chain.

Shumacker inserts 1 needle 10 cm off the spine of L-2 at a 30° angle toward the median sagittal plane and directs it to clear the anterolateral margin of the vertebral body and to place its tip in front of the psoas muscle. He finds that 10-ml volumes extend from L-1 through L-3. I have used Shumacker's technic and appreciated its advantages for the past 10 years. If one attaches a syringe filled with a few ml of air and solution to the needle, he can feel the "loss of resistance" as the needle tip leaves the psoas muscle, when it is correctly placed.

Löfström inserts 1 needle (at L-2) or 2 needles (at L-2 and L-4), 7 to 10 cm off the midline. However, he first aims at the transverse process, as in the classic methods. He blocks the lumbar chain with 1 injection of 15 ml.

The proximity of the kidney may be a disadvantage to the L-2 route. However, Shumacker's diagram and my experience suggest that if one carefully observes his landmarks, the needle only pierces the muscular mass (sacrospinalis, quadratus lumborum, and psoas) and remains medial to the kidney. Dr. Brown's excellent paper should encourage anesthesiologists to try this valuable approach.

Ray J. Defalque, MD
Department of Anesthesiology
Indiana University School of Medicine
Indianapolis, Indiana

REFERENCES

1. Reid W, Watt JK, Gray TG: Phenol injection of the sympathetic chain. Br J Surg 57:45-50, 1970

2. Shumacker HB Jr: Sympathetic denervation of the extremities. Curr Probl Surg 1965

3. Löfström B: Lumbar sympathetic block, Illustrated Handbook of Local Anesthesia. Edited by E Erickson. Chicago, Year Book Publishers, 1969, pp 140-144

* * * * *

To the Editor:

Dr. Defalque correctly points out that a number of lateral approaches have been described for lumbar sympathetic block. All of them, however, are either performed at the level of L-2 or involve more than a single needle. Of greater interest, however, is the fact that Dr. Reid states, "Puncture of the kidney sometimes occurs and is recognized by a pendulum swing of the needle or by the escape of urine through the needle. The presence of peri-ureteric fibrosis at subsequent ganglionectomy has occasionally been seen and it is possible that urinary symptoms may occur owing to ureteric damage." He does go on to say that in most cases the symptoms are transient and full recovery results. But the point is, that damage to the kidney is certainly possible if one uses a wide lateral approach at either L-2 or L-3.[1] The lateral approach described by us at L-4 precludes the possibility of damage to the kidney while still providing effective blockade of the lumbar sympathetic chain.

Eli M. Brown, MD
Department of Anesthesiology
Sinai Hospital of Detroit
Detroit, Michigan

REFERENCE

1. Reid W, et al: Phenol injection of the sympathetic chain. Br J Surg 57:45-50, 1970

To the Editor:

I read with interest the article on the single-needle lateral approach for lumbar sympathetic block by Drs. Brown and Kunjappan. Dr. Donald P. Todd and I have frequently performed single-shot and continuous-catheter lumbar paravertebral sympathetic block for reflex sympathetic dystrophy of the lower extremities. Our technic involves the taking of a scout PA x-ray film of the lumbar spine with an 18-gauge needle positioned on the skin at the upper edge of the 2nd lumbar spinous process. After identifying the proper level, the skin is prepared with an antiseptic solution and draped in a sterile manner. A skin wheal is raised 5 to 6 cm lateral to the upper edge of the spinous process of the 2nd lumbar vertebra.

A 20-gauge, 12.5-cm needle is then placed through the skin wheal and contact made with the transverse process of the 2nd lumbar vertebra. The marker on the needle is set a distance of 3 to 4 cm from the skin surface before redirecting the needle medially and cephalad so that it slides off the upper border of the transverse process and the lateral aspect of the vertebral body. By sliding off the upper border of the transverse process, painful paresthesias to the lateral thigh (L-2) are avoided. The position of the needle is verified by PA and lateral x-ray films before injection of 20 ml of anesthetic solution.

Similarly, multiple encounters with the periosteum and blockade of the 2nd lumbar somatic nerve should not be a problem. Multiple periosteal contacts can be considerably reduced by taking an initial scout x-ray film and accurately locating the site of needle insertion. Also, the hypalgesia in the area of the 2nd lumbar dermatome seldom interferes with the diagnostic or therapeutic values of the block.

By following the classic approach, we have not found it necessary to use the wide lateral approach for lumbar sympathetic blockade. A single needle with its point at the anterolateral aspect of the 2nd lumbar vertebra is sufficient to precisely and reliably block the lumbar paravertebral sympathetic chain.

Frank A. Takacs, MD
Department of Anesthesia
Massachusetts General Hospital
Boston, Massachusetts

In each issue of the Journal an article of particular interest and value to anesthesiologists, which has been published elsewhere, will be presented. Primarily the material will contain fundamental basic information which has been presented by anesthesiologists, physiologists, pharmacologists, and others and, on occasion, by commercial firms. In the last instance, these reprintings are not to be construed as an endorsement of the particular commercial firm or its product by Anesthesia and Analgesia—Current Researches.

Fundamental Principles for Preparing Psychology Journal Articles*

HARRY F. HARLOW†
University of Wisconsin

As retiring Editor of the *Journal of Comparative and Physiological Psychology*, I feel that I have one remaining responsibility to my psychological colleagues. Having passed judgment on about 2,500 original manuscripts and almost as many revisions in my 12 years as Editor, I believe I should bequeath to posterity some principles of scientific reporting that I have formulated only through countless hours of moonlighting.

COVERING LETTER

In plotting the publication of a manuscript the prospective author should think first about the covering letter. It is an unforgivable error to write, "I am submitting a manuscript for your consideration. . . ." This evasive method gets you nowhere with editors. Even if the nondirective technique works with many patients, there are some sick people who are best approached using positive measures.

There are a number of general principles underlying a good covering letter, and they can be illustrated by example. I offer the following:

DEAR HARRY:

I am submitting the manuscript, "Creative Thinking by Paramecia," for publication in JCPP. My chairman has assured me that upon acceptance of this manuscript he will recommend me for promotion to associate professor. Two recipients of the Distinguished Psychologist Award have reviewed this paper and recommend it highly.

I am pleased to see that you are one of five candidates for President of the American Psychological Association. As you know, I have nominated you for many years and will probably give you my support in the future.

Because of the unusual significance of these researches, I would like early publication, which I will finance from my National Institute of Mental Health grant.

Warm Regards,

John Hopeful
Assistant Professor

The battle is now half won. You will get a fair shake.

*The publication costs for this report were borne by the American Psychological Association.

†*Still* at the University of Wisconsin.

Copyright 1975 by the American Psychological Association. Reprinted by permission of publisher and author.

INTRODUCTION

Almost all scientific papers include an introduction even though large parts of it are frequently buried in the sections labeled Method and Results. However, the total omission of an introduction constitutes a glaring error, and, anyway, it is fun to write introductions—one is not constrained by facts.

One way to write an introduction is simply to state what the experiment is all about and make predictions about the outcome. Since the data will already have been collected and processed, you will have no difficulty in making insightful predictions. As all famous historians know, one can predict the past with great precision. However, prediction is one of the great booby traps into which young and inexperienced psychologists often fall. All their predictions are confirmed; older men know that this never happens. The proper technique is to select the prediction of minimum import, or throw in a completely extraneous one, and have this prediction fail. Honesty is the best policy.

Although some psychologists write simple, straightforward introductions, this is commonly considered to be *déclassé*. In the sophisticated or "striptease" technique you keep the problem a secret from the reader until the very last paragraph. Indeed, some very sophisticated authors keep the problem a secret forever. Since I am interested in readers as well as authors, I advise that readers always approach introduction sections using the Chinese technique—begin at the end and read backward.

The function of the introduction is to impress your colleagues with your scholarship and erudition—academic appointments are seldom made on the basis of a results section. Scholarly one-upmanship is attained with an unending number of nonspecific references, such as:

"The up-and-down effect was first discovered by (_____, 1762) and this study led to many fruitful investigations (_____, 1804; _____, 1827; _____, 1844; _____, 1861; _____, 1874; _____, 1888; _____, 1894; _____, 1911; _____, 1917; _____, 1928; _____, 1937; _____, 1944; and _____, 1952). Beyond these researches the broad implications of this discovery led to related studies on the in-and-out phenomenon (_____, 1829; _____1855; _____, 1888; _____, 1914; _____, 1927; and _____, 1950), and the around-and-about law (_____, 1884; _____, 1914; __, 1933; _____, 1947; _____, 1952; _____, 1952, and _____, 1960)."

Often, but not often enough, young and lazy authors are frightened away from this technique simply because they are appalled by the amount of work involved in reading the literature, especially if part is written in some foreign language. However, there is no excuse for this attitude; the author should remember that he is not reading the literature—just citing it. Anyway, he can always rely on some scholarly article in *Psychological Bulletin* as a secondary source to provide an impressive reference list with almost no effort.

Occasionally editors object to overly extended, striptease introductions and to long lists of nonspecific references. At this point the author should take the bull by the horns and write the editor a nasty letter accusing him of rigidity, illiteracy, and lack of scholarly interests. Editors are busy and editors are human. They can be broken—don't pamper them.

METHOD

To write a good Method section, one must be an idealist. If this section is to be understood, it must be clear, orderly, and systematic. The best way to achieve this is not to tell what really happened, or if you must tell, wait as long as is physically possible. Your four groups of *Ss* should always add to 20 or 30 each. If 7 *Ss* in Group 2 died of pneumonia and 19 *Ss* in Group 3 were suffocated, don't put it in the Method section. The death of these *Ss* was not planned but resulted, and the information obviously belongs in the Results. There is also good reason for putting this information in the Discussion because you can then mediate on how different the results might have been had the *Ss* lived.

A mechanical problem that often creeps up in Method relates to the spelling and meaning of words such as "maize," "liman," and "maccaccuss resus." Fortunately there is a fundamental rule. Writing manuscripts is a tedious process and time means money. You must protect your time in every possible manner. If you cannot spell or do not know the meaning of a word, don't look it up in *Webster's Third New International Dictionary*. If the word isn't in Thorndike and Barnhart, 95% of your psychological audience won't know the meaning of the word or how to spell it anyway. Moreover, that's the Editor's responsibility. Let well enough alone.

RESULTS

The Results section comes in a very convenient place, and one way to start it is to put the procedures which you inadvertently omitted from the Method section—which you are too lazy to rewrite—at the very beginning of the Results.

If the Editor objects, point out that you are doing this for the sake of continuity. The next problem can only be resolved by reference to the Procedure. Reread the Procedure section and find out the order that you said you were going to follow; then, carefully rearrange that order in the Results. If you write succinctly and clearly, there is a real danger that the reader will only read your manuscript once, and every psychologist worth his salt recognizes the importance of overlearning. Then, too, if he has to struggle to understand it, he will naturally attribute the difficulties to the abstruseness of the problem.

The most important items in the Results will probably be the figures. Authors seldom realize the importance of figures and consequently fail to give them sufficient attention. It is absolutely imperative that the figures be of professional quality. This may cost a little money, but even with academic salaries what they are, the cost is cheap compared with the value of the man-hours spent in gathering and processing the data. The ordinate and abscissa should be boldly drawn and the curves should stand out like sore thumbs, which they frequently really are.

Now we are at the critical point. It is important to make sure that all legends, all numbers on the ordinate and abscissa, and all titles are completely unreadable. If you fail to do this, there is a real danger that editors and readers will compare the information given in the graph with what is written in the Results and Discussion and call the discrepancies to your attention. Fortunately your figures can be made unreadable at a high academic level by following a few simple rules. Draw the figure on paper 2 ft. sq. and never purchase templates with letters more than ¼ in. high. Then when the figures are reduced in size for Journal publication, the data will remain a personal secret. You can subsequently let out the data you are not trying to hide by personal correspondence.

Even authors who follow this rule—and the general principle is widely understood—frequently make a completely unforgivable error by sending glossy prints of their figures to the Editor. If the Editor has already recognized the fact that he has presbyopia and has purchased glasses, he may insist that the graphs be redrawn, and then the jig is up. However, if you send the original drawings and simply scratch out in pencil the copy for the carbon which some editors require, you have a high chance of success. A better technique is to send the carbon without figures. Most editors will relay this carbon to a consulting editor without checking for figures, and a single favorable review frequently insures publication.

Another good technique is to supplement the figures by presenting the data for individual animals in lengthy tables without means, medians, or standard deviations. No reader, and certainly no editor, will ever take the trouble to make the necessary computations to check your curves or statements of significance. The additional advantage is that long, detailed tables carry the implication that you engaged in an overwhelmingly complicated piece of research.

DISCUSSION

Whereas there are firm rules and morals concerning the collection and reporting of data which should be placed in the Results, these rules no longer are in force when one comes to the Discussion. Anything goes—shoot the moon—the sky's the limit!

Even though one is going far afield, the endeavor should not be random, but the deception should be achieved with skill and grace. The most important fundamental guiding principle is to repeat the predictions made in the introduction—elaborating them if possible—and then to describe the importance of your work in broad generic terms and never get down to mundane fact. In Discussion sections one does not discover things about maze performance, minutes to run down a straight alley, 48 hr. of food deprivation, or the number of mechanical puzzle devices opened—one makes breathtaking discoveries about learning, drive reduction, motivation, and curiosity. After all, this is the way psychologists are going to talk when they present and discuss their work at scientific meetings, and no man attains fluency in the jargon without practice.

Very occasionally some psychologist makes the mistake of saying what is worth saying in the Discussion and then stopping. This is interpreted by other psychologists as

indicating that the person lacks verbal skill and creativity. Anyone can talk effectively about data which actually exist.

If your experiment has any merit whatsoever, and little is required, there is the likelihood that someone else will do it later and do it better. To save face it is important to engage in the alibi-in-advance technique. Endless Discussion pages can be consumed by describing how you would do the experiment if you were to do it over, and the joy of this device is that no data need be collected. You have the fellow who is going to be so cold and calculating as to check your results, on the run, and if you are smart enough, no matter what he obtains, it will be a dry run.

Even if you have only completed a single experiment you can greatly augment your data by several pages of description of the results which you would have obtained had you done a long series of related experiments. Furthermore, a clarity is achieved by describing the experiments that were not done instead of those that were because the results in the imaginary experiments come out in an integrated, orderly manner that is seldom achieved in the laboratory. Remember that data collection is a routine process and the brilliant scientist will rise above it when he comes to the Discussion.

Nothing is now left except to find a way to end the Discussion section, which has become so long and so confused that most readers will have forgotten what the original problem was about anyway. Discussions should be concluded in a friendly, charitable, and slightly condescending manner. First, say a few little things about the difficulties of doing research, particularly research in your chosen area. Then point out that there are a few little technical problems and research odds and ends that need to be picked up before your area of choice is completely neat and tidy. Finally, explain that once the research trail has been broken, less strong bodies can follow along.

FOOTNOTES

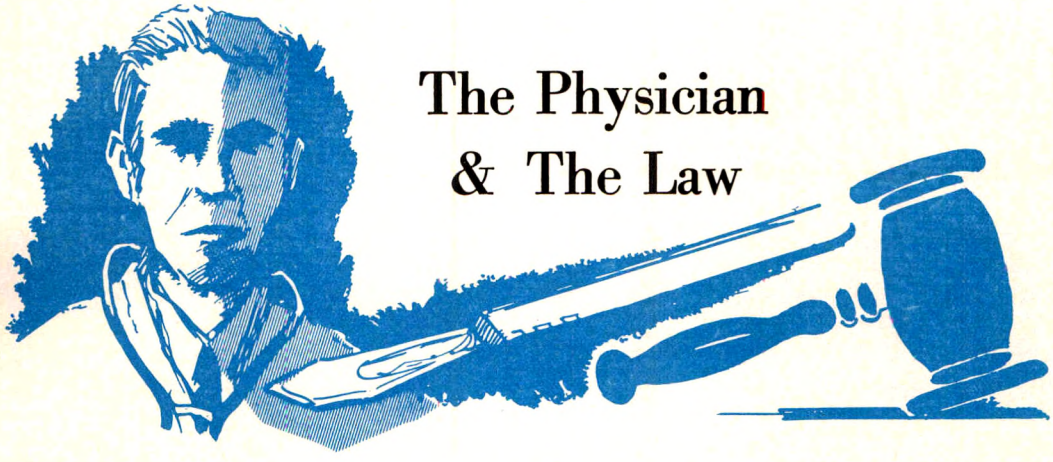
Finally, one comes to the footnotes. Footnotes are always on a separate page (or pages) and there is a chance that the Editor will miss them, particularly if the typewritten material is single-spaced and turned upside down. Thus, here is an opportunity to introduce a couple of additional pages of complete trivia. If the Editor should discover them, nothing will be lost, for paper is cheap. Remember that this is your last chance to get in some padding, and never forget the fact that promotion is the prerogative of deans and final decisions are frequently weighed on other scales than those of justice.

Special attention should be given to one footnote—the acknowledgment. It is this one that separates the men from the boys. Since most experiments are not worth doing and the data obtained are not worth publishing, great care should be taken to protect one's reputation when one's name is associated with the conventional potboiler. This can be achieved by a simple and honest footnote.

"The author (or authors) had very little to do with this research. The idea was stolen from Dr. _____, the experimental design was proposed by my (our) statistical consultant, Dr. _____, the *S*s were run by Mr. _____ and Miss _____, the data were processed by the mathematical computing center, and the paper was completely rewritten by Editor _____, on the basis of extensive notes and suggestions made by Consulting Editor _____, whose name was inadvertently left off the masthead of the *Journal of* _____."

EDITORIAL POLICY

Faced with a mounting flood of uninspired researches and watching publication lag continuously mount despite multiple allotments of additional *Journal* pages, I came to realize that my editorial policies, even though rigid and unreasonable, were incomplete or else in error. For a long time I thought there was no solution, and then I realized I was wrong. I established a new *JCPP* policy and formalized it with a rubber stamp, only to realize that my term as Editor had already expired. But at least I have the rubber stamp which I planned to use on a large number of manuscripts: "Not read but rejected."



The Physician & The Law

No Negligence in Surgeon's Failure to Supervise Anesthesiologist

THE widow of a patient who died during preparation for a laminectomy sued the surgeon, the anesthesiologist and the hospital. The hospital settled for $20,000 and the anesthesiologist for $210,000 prior to trial. A California jury decided in favor of the surgeon.

The widow contended that the surgeon had negligently failed to supervise the anesthesiologist properly. She further contended that the surgeon failed to administer resuscitation to her husband promptly.

The surgeon contended that supervision of the anesthesiologist was not his responsibility. He said that resuscitation was administered in a timely and proper manner. —*Holquia v. Mission Hospital* (Cal.Super. Ct., Los Angeles Co., Docket No. SEC 10263, Feb. 24, 1975)

Reprinted with permission from THE CITATION published by the Law Division of the American Medical Association.

Questions and Answers

We invite you to submit questions to the Editorial Office, Kahler East, Suite C, Rochester, Minnesota 55901. The names of those submitting questions will remain anonymous if so desired.

The answers will be prepared by competent authorities, and their names will or will not appear, according to their specific wishes.

Ronald W. Dunbar, M.D.
Contributing Editor
Atlanta, Georgia

* * *

QUESTION: *Atropine up to 0.6 mg given as premedication to patients with glaucoma is usually considered not harmful, because of its small amount. During the process of reversal of nondepolarizing muscle relaxants, atropine is frequently given in conjunction with antagonists in doses of 1.5 mg or 2 mg. Is this considered safe?*

MD, Ohio

ANSWER #1: Atropine has long been incriminated as an anticholinergic agent responsible for the production of angle-closure glaucoma when administered systemically, with very little substantiating evidence.[1] Certainly, topical atropine, by increasing pupillary block and producing mydriasis, crowding the iris into the predisposed anatomically narrowed angle, can produce angle-closure glaucoma.

Systemic administration of the usual preanesthetic doses of atropine (0.6 mg) has been said to be safe even in anatomically predisposed eyes.[2]

Administration of large doses of atropine in conjunction with the use of prostigmine (or similar drugs) during the process of reversal of nondepolarizing muscle relaxants at varying planes of anesthesia is a much more complex problem. There is an amazing paucity of information regarding pupil size during this process. In the eye with an angle predisposed to develop angle-closure glaucoma, any mydriasis may precipitate an attack of angle-closure glaucoma. Rosen[3] feels that the dangers are mythical. He compares the amount of systemically administered atropine reaching the eye to the amount available to the eye with the administration of a single drop of 1% atropine solution topically. Extending his calculations for 2 mg of atropine given systemically and evenly distributed in a 70-kg individual, only 0.0004 mg reaches the entire eye as compared to 0.6 mg of atropine available to the eye when a single drop of a 1% solution is applied to the eye.

Practically, the fear of producing an attack of acute angle-closure glaucoma can be dispelled by administering topical pilocarpine solution (2%) to produce miotic pupils preatropinization[4] or using morphine as a preanesthetic agent, which also produces a profound miosis. In any patient with known glaucoma, either angle-closure or open angle, continuation of glaucoma medication before, during, and after operation is advised. In the recovery room, an evaluation of the pupils with respect to size, symmetry, and shape would confirm the absence of angle-closure glaucoma. If the pupils are irregular, asymmetric, and mid-dilated, an ophthalmologic consultation should be obtained to medically control and eventually surgically correct the attack of angle-closure glaucoma.

REFERENCES

1. Duke-Elder S: System of Ophthalmology. London, Henry Kimpton, 1972, 14:1304-1308

2. Schwartz H, de Roetth A Jr, Papper EM: Preanesthetic use of atropine and scopolamine in patients with glaucoma. JAMA 165:144-146, 1957

3. Rosen DA: Anesthesia in ophthalmology. Can Anaesth Soc J 9:545-549, 1962

4. Grant WM: Toxicology of the Eye. Second edition. Springfield, Illinois, Charles C. Thomas, Publisher, 1974, pp 163-168

John C. Rieser, MD
Chief, Glaucoma Service
Department of Ophthalmology
Emory University School of Medicine
Atlanta, Georgia

ANSWER #2: *Atropine* in these doses would tend to dilate the pupils and paralyze the ciliary muscle. *Neostigmine* has the opposite effect, tending to constrict the pupil and cause the ciliary muscle to contract. Where the balance might lie between these two antagonistic actions would determine the resultant total effect on pupil and ciliary muscle. It would be interesting to have data from observations on patients under these special circumstances to determine where the balance generally lies. This could easily be done by measurement of the size of the pupils, and one could estimate that the ciliary muscle was being affected in a similar manner.

In patients with *chronic open-angle glaucoma*, if the balance were far in the direction of dilation of the pupil and paralysis of the ciliary muscle, one should not be surprised if the intraocular pressure becomes elevated, but in this kind of glaucoma and under these special circumstances, one would expect that the amount and duration of elevation of intraocular pressure would rarely be enough to cause permanent damage to the eye. If the patient was receiving antiglaucoma medications, such as miotic eyedrops and systemic carbonic-anhydrase inhibitors, one would expect less elevation of intraocular pressure.

In the great majority of patients with chronic open-angle glaucoma under ordinary treatment, and who do not have far-advanced loss of vision from their glaucoma, one would expect the risk to vision to be negligible, but to establish whether this opinion is valid, a clinical study is needed in which not only the pupils are measured but also the intraocular pressure (by tonometer), and the visual fields before and several days after the procedure, when the effects of neostigmine and atropine were gone.

In patients with chronic open-angle glaucoma, the risk is negligible, but there is a small category of patients in whom the anterior chamber of the eye is abnormally small and shallow anatomically, and who without treatment may maintain normal intraocular pressure. If their pupils are dilated, they may very rapidly develop *acute angle-closure glaucoma*. This form of glaucoma threatens the eye with severe damage and potentially irreversible loss of vision within 2 or 3 days if unrecognized and untreated. Presumably, such patients would be at risk only if the antagonistic effects on the pupil by neostigmine and atropine resulted in noticeably dilating the pupil.

It is difficult to identify people in advance who may develop acute angle-closure glaucoma if their pupils are dilated, but if the anesthesiologist or internist learns to recognize by looking carefully at the depth of the anterior chamber (distance from cornea to iris) with the aid of a small beam of focused light, the chances of identifying these individuals can be increased, and an evaluation by an ophthalmologist can be obtained for the occasional person with conspicuously shallow anterior chambers. Prophylactically, the ophthalmologist may wish to prescribe pilocarpine eyedrops of low concentration and a carbonic-anhydrase inhibitor.

Persistent enlargement of the pupils, and, especially, unequal enlargement and irregular enlargement (so that the pupil is not round) are the foremost basis for suspicion and for tonometric measuring of intraocular pressure. One should not count on the patient to complain about decrease of vision or pain in the eye, since patients in the critical period after anesthesia are notoriously unreliable in recognizing and reporting these symptoms.

REFERENCES

1. Lazenby GW, Reed JW, Grant WM: Short-term tests of anticholinergic medication in open-angle glaucoma. Arch Ophthalmol 80:443-448, 1968

2. Lazenby GW, Reed JW, Grant WM: Anticholinergic medication in open-angle glaucoma. Long-term tests. Arch Ophthalmol 84:719-723, 1970

3. Grant WM: Toxicology of the Eye. Second edition. Springfield, Illinois, Charles C Thomas, Publisher, 1974, pp 144-148

4. Goodman LS, Gilman A: The Pharmacological Basis of Therapeutics. Fourth edition. New York, The Macmillan Company, 1970, pp 458-459

John C. Snow, MD
Department of Anesthesiology
Boston University School of Medicine and University Hospital
Boston, Massachusetts

* * *

QUESTION: *It is well known that food and water pass over the tongue and into the esophagus without triggering the gag reflex. Equally well known is the fact that a foreign object such as one's finger or a laryngoscope blade does trigger the gag reflex when it touches the same portion of the tongue (in the unanesthetized patient).*

Please explain the neuromuscular and other factors that prevent the activation of the reflex in the presence of food, yet cause activation in the presence of a foreign object.

MD, Oklahoma

ANSWER #1: In humans, the areas of maximum sensitivity to the second, or pharyngeal, stage of swallowing are the anterior and posterior pillars of the fauces and the tonsils. The sensory nerve for the pharyngeal stage of swallowing is basically the glossopharyngeal nerve.[1] The areas of maximum sensitivity to the gag reflex are the fauces, base of tongue, palate, and posterior pharyngeal wall. The sensory innervation for the gag reflex is also the glossopharyngeal nerve, with contributions from V and X.[2]

The glossopharyngeal afferent fibers include both fibers that elicit the gag reflex and fibers that inhibit the gag reflex. The inhibiting fibers of the 9th nerve respond to milder stimuli than do those fibers which call forth the gag reflex.[2] Therefore, mild stimuli, such as small amounts of water, salivary secretions, or food, will inhibit the gag reflex and stimulate the second, or involuntary, stage of the swallow reflex. Stronger stimuli, such as accumulated saliva or a large bolus of food, will stimulate the gag reflex. In addition, the gag reflex is influenced by fibers that pass to and from the coordinating center in the medulla oblongata to the cerebral cortex, thus giving rise to the gag reflex secondary to repulsive sights or odors received from the eyes, nose, and mouth.[3] The course of the exact neuropathways from higher centers to the medullary centers is still unclear.[4]

In unanesthetized individuals, cortical influences, as well as the degree of stimulation by a finger or laryngoscope, account for the triggering of the gag reflex. The reflex may be inhibited by asking the patient to quietly breathe in and out, a phenomenon thought to be secondary to respiratory inhibition of the gag reflex via a final common pathway.[2]

REFERENCES

1. Best CH, Taylor NB: The Physiological Basis of Medical Practice. Baltimore, The Williams & Wilkins Company, 1966

2. Khan AE: Gagging. Dent J Aust 21:188, 1949

3. Faigenblum MJ: Retching, its causes and management in prosthetic practice. Br Dent J 125: 485-490, 1968

4. Schapiro H: Retching responses in Caiman sklerops elicited by central nervous stimulation. Proc Soc Exp Biol Med 129:917-920, 1968

Ronald G. Dennis, MD
John J. Per-Lee, MD
Department of Otolaryngology
Emory University School of Medicine
Atlanta, Georgia

* * *

ANSWER #2: This question should occur to every anesthesiologist but seldom does, or at least is seldom voiced. It did occur to Wassilieff,[1] who noted on himself that tactile stimulation of the soft palate inhibited swallow, and, in longer continuation, elicited nausea and retching. In the monkey, swallow is found to be alternative to retching as a response to continued stimulation of the superior laryngeal nerve.[2]

As stated by Doty and Bosma,[3] stimulation of afferents in the pharyngeal area is pluripotential, deglutition being but one of several effects obtainable. These authors suggested that such functions as chewing, licking, coughing, sneezing, gagging, and respiration, which overlap in their afferent and efferent channels, may interact with swallowing, but, as expressed by Bosma (personal communication, 1975), swallow and, apparently, the associated feeding composite, so dominate the bulbar area that alternative elicitations are inhibited.

Of cognate interest is the well-established roentgenologic observation[4,5] that when radiopaque liquid is swallowed, a little material frequently penetrates the entrance of the laryngeal vestibule, only to be expelled later by hyperelevation of the larynx against the inverted epiglottis, in a kind of squeeze action. Absence of a cough reflex during this period is usually attributed to the mode of association of the reflex centers of the medulla, which is thought to render the major reflex actions mutually exclusive.[6] The burst of coughing occasionally evoked with a swallow suggests to me that this explanation is not the whole story, and that another mechanism may sometimes also be involved.

A bunched-up appearance at the entrance is observable laryngoscopically in prolonged effort closure of the larynx (complete laryngeal spasm), and probably results in part from inversion of the mucosa by aryepiglotticus muscle fibers ending in the mucosa. In swallow, such inversion removes cough-originating receptors from contact

with vestibular bolus. Incompleteness of the inversion or of the above-mentioned squeezing action could explain a cough triggered at this time.

Finally, cineradiography[4] shows that about 0.5 second elapses between the time the leading edge of a bolus passes the fauces and the time the trailing edge enters the esophagus. If the period of stimulation of gag-originating receptors necessary to elicit a gag reflex exceeded 0.5 second, the apparent suppression of gag by swallow would again be accounted for.

REFERENCES

1. Wassilief N: Wo wird der Schluckreflex ausgelöst? Z Biol 24:29-47, 1888

2. Doty RW: Influence of stimulus pattern on reflex deglutition. Am J Physiol 166:142-158, 1951

3. Doty RW, Bosma JF: An electromyographic analysis of reflex deglutition. J Neurophysiol 19:44-60, 1956

4. Saunders JB deCM, Davis C, Miller ER: The mechanism of deglutition (second stage) as revealed by cineradiography. Ann Otol Rhinol Laryngol 60:897-916, 1951

5. Ramsey GH, Watson JS, Gramiak R, et al: Cinefluorographic analysis of the mechanism of swallowing. Radiology 64:498-518, 1955

6. Bosma JF: Deglutition: pharyngeal stage. Physiol Rev 37:275-300, 1957

B. Raymond Fink, MD
Anesthesiology Research Center
University of Washington
Seattle, Washington

* * *

QUESTION: *1. Does the patient have the right to request the Professor of Anesthesiology or one of the senior anesthesiologists to perform the intubation or any other anesthetic procedure rather than one of the professor's students? 2. What are the possible legal consequences following this request?*

MD, Belgium

ANSWER #1: The question relates to the contract for patient care embodied in the physician-patient relationship. Belgium is a civil-law country; my answer is couched in terms of the common law of the USA and countries of the British Commonwealth. The legal principles should be similar, however.

Patients who enter teaching hospitals are under constructive notice that a major portion of their care will be given by trainees, acting under staff supervision. It is common knowledge among the American public (and, I assume among citizens of other countries as well) that a university hospital is engaged in teaching and that house officers and even medical students participate actively in patient care. Thus, if the patient does not request the service of a specific staff physician, it is customary practice to allow residents to perform such tasks as laryngoscopy and endotracheal intubation, as well as to select and administer the anesthetic agent.

If a patient inquires of the staff as to who will be caring for him, he must be apprised frankly and honestly. The patient does have the right to request the services of a staff physician. This is so because the contract for medical care, embodied in the physician-patient relationship, is a personal-services contract. As such, the duties emanating from it cannot be delegated without the express consent of the parties. If a physician unilaterally delegated to others any of his duties to the patient, especially to someone less skilled than he, he could be liable for fraud or breach of contract. The delegatee could also be liable for battery, since he performed a service that the patient had not authorized him to carry out.[1]

As with many other aspects of medical care, absent emergency circumstances, it is highly desirable that the patient's wishes be followed.

REFERENCE

1. Dornette WHL: The physician-patient relationship, Chap. 2; Holman EJ: Consent to treatment, Chap. 12; and Dornette WHL: A Medical Accident Prevention Program, Chap. 26 in Dornette WHL: (ed) Legal Aspects of Anesthesia. Phila. Davis, 1972, pp 17, 18, 180-183, 473

William H. L. Dornette, MD, JD
Division of Anesthesiology
The Cleveland Clinic
Cleveland, Ohio

* * *

ANSWER #2: The answer to the first question is yes; to the second, the professor, qua physician, ignores his patient's requests at his financial peril.

The fact situation falls within the Anglo-American Common Law doctrine of Consent (conversely, assault and battery). Each individual has the right to designate who may touch him and to what extent. This right to bodily integrity is not only nearly absolute but is also jealously guarded by the courts.[1] The patient's right to bodily integrity lets him choose both who may and may not

administer anesthesia to him (and intubate his trachea), either implicitly or explicitly.

If the professor, qua the patient's personal anesthesiologist, lets the student intubate his trachea against the patient's explicit request to the contrary, the student is guilty of a battery (an unlawful touching). If uninjured, the patient-plaintiff is entitled to nominal money damages. If injured, the patient is entitled to compensatory money damages commensurate with the injury. If the patient-plaintiff's rights were willfully and wantonly abused, punitive damages can also be awarded—often 3 times the compensatory damages. If the professor helped (touched), the same analysis applies.

On the other hand, if the professor watched as the student intubated the patient-plaintiff's trachea, the patient would be hard pressed to allege and prove that the professor committed a battery. However, the professor can probably be sued successfully under several other legal theories: negligence; abandonment; fraud and deceit; contract.

"Negligence" requires the patient-plaintiff to have been injured. The gist is: The professor had the duty to do the intubation himself or turn it over to a competent anesthesiologist; the professor did neither; as a direct result, the patient was injured. The professor pays.[2]

The gist of abandonment is that, because the patient-physician relationship has been established, the professor, qua physician, has the duty to personally care for (intubate) his patient. The professor breached that duty to the patient's detriment.

"Fraud and deceit" requires the patient-plaintiff to prove that the professor led him to believe that he would do the intubation, while all the time, the professor intended and knew the student would do it.[3]

Under a contract theory, the patient-plaintiff must allege and prove that the professor made an oral contract to personally anesthetize (intubate) the patient; that the professor did not do so. The patient-plaintiff is, therefore, entitled to damages for breach of contract.

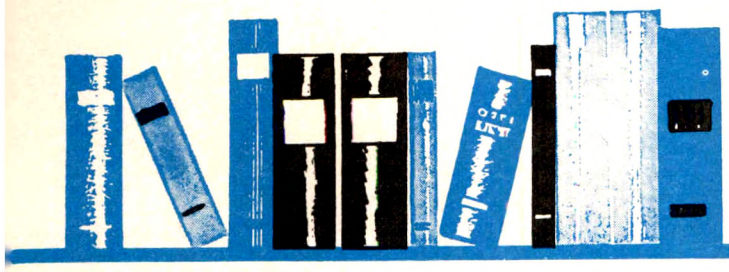
REFERENCES

1. Mohr v Williams, 95 Minn 261, 104 NW 12 (1905)

2. Prosser WL: The Law of Torts. Fourth edition. St. Paul, Minnesota, West Publishing Company, 1971, pp 143-149

3. Prosser WL: The Law of Torts. Fourth edition. St. Paul, Minnesota, West Publishing Company, 1971, pp 699-720

Charles W. Quimby, Jr, MD, LLB
Department of Anesthesiology
Vanderbilt University
Nashville, Tennessee



the book shelf

Paediatric Anaesthesia, Second Edition—Davenport, Harold T., MB, FRCP(C), FFARCS. Chicago, Year Book Medical Publishers, Inc, 1973, 258 pp.

This monograph has been written by an anesthesiologist with great clinical experience in pediatric anesthesia. Short and easily readable, this book encompasses a broad overview of the subject.

Some of the contents seem too basic: drawings of venipuncture technics, for example. However, the chapter entitled "The Child Patient" is particularly well done and should be of interest to any anesthesiologist who deals with children. The physiologic and physical differences of the pediatric as compared with the adult patient are briefly but well summarized.

Anesthesia for major operations and for patients with rare conditions is dealt with quite superficially. An anesthesiologist would likely find this book only a starting place were he to deal frequently with major pediatric cases.

This book could be of interest to anesthesiology residents and as a refresher for those who care for pediatric patients on a limited basis.

Wilbur F. Cant, MD
Department of Anesthesiology
Mayo Clinic
Rochester, Minnesota

* * *

Treatment of Pain—Voris, Harold C., MD, PhD, and Whistler, Walter W., MD, PhD, Editors. Springfield, Charles C Thomas Publishers, 1975, 161 pp, price $14.00.

The editors of this book have assembled a number of presentations on the treatment of chronic intractable pain. The presentations were made at a pain-treatment symposium sponsored by the Department of Neurological Surgery, Rush Medical College, Rush-Presbyterian-St. Luke's Medical Center, Chicago. The contributors are noted authorities on the current practices of treating chronic pain problems.

Although the book is primarily oriented toward the surgical technics of pain management, other modalities such as acupuncture, hypnosis, and drug therapy are also covered.

The material presented in this book is easily readable and understandable. The information presented will be beneficial to anyone interested in the clinical management of chronic pain problems.

Lee A. Nauss, MD
Department of Anesthesiology
Mayo Clinic
Rochester, Minnesota

* * *

Fluids for Anesthesia and Surgery in the Newborn and the Infant—Bennett EJ. Springfield, Illinois, Charles C Thomas, Publisher, 1975, 205 pp, price $18.50.

This comprehensive book should fill a long-standing void in the field of pediatric anesthesia. Dr. Bennett and contributors, Drs. Dalal, Ramamurthy, and Schmidt, have done an outstanding job in writing it.

Chapter 2, "The Newborn," is alone worth the price of the book. Dr. Bennett details what is known about neonatal renal function and various fluid regimes that have been proposed to meet the needs of the neonate. This is a controversial area and

the question of the quantity and especially the electrolyte content of fluids to be administered has long been debated. Dr. Bennett very logically presents the facts that:

1. The neonatal kidney is quite mature in its function and

2. Can concentrate urine and

3. Fails to conserve sodium in the presence of a sodium deficiency.

With this in mind, he gives a rationale for the use of multielectrolyte solutions in the neonate.

Although the book contains only 205 pages, it is extensive in its coverage of the subject. Readers will find a most complete chapter on pyloric stenosis and the ramifications of fluid therapy in this commonly encountered entity. Other problems, including omphalocele, ruptured bowel, colostomy, congenital diaphragmatic hernia, to name but a few, are also covered succinctly, if not as completely. The chapter on intravenous alimentation, by Dr. Ramamurthy, should be especially interesting to pediatric anesthesiologists, who are usually not concerned with this technic and its problems.

The book is to be recommended to all interested in pediatric anesthesia. However, the reader should not plan to get through it quickly, as a large amount of detail is covered. It should be of help to all who care for neonates and infants, both intraoperatively and perioperatively.

W. F. Cant, MD
Department of Anesthesiology
Mayo Clinic
Rochester, Minnesota

* * *

Acupuncture Anesthesia (A Translation of a Chinese Publication of the Same Title). Miami, U.S. Directory Service, 1975, 340 pp, price $30.00.

Acupuncture analgesia (not anesthesia) has been practiced in China for a number of years with varying degrees of success. The original Chinese text was prepared by several investigators and practitioners in Shanghai. It consists of historical backgrounds, empirical technics of acupuncture analgesia for various surgical procedures, and speculation on the hypotheses of mechanism of action.

The difficulties of acupuncture analgesia include unknown mechanisms, lack of standard technics, and inconsistent results; it is an interesting procedure and may have some practical value in extremely rare instances.

Information in the book is believed reliable, but its accuracy and completeness should not be accepted without additional data obtained from further scientific investigation. It is hoped that the book will lead to further investigation and a better understanding of the subject.

Josef K. Wang, MD
Department of Anesthesiology
Mayo Clinic
Rochester, Minnesota

* * *

Electroanesthesia: Biomedical and Biophysical Studies—Sances, Anthony, Jr. and Larson, Sanford J. New York, Academic Press, 1975, 367 pp, price $36.00.

Recently, considerable evidence has been accumulated to demonstrate the clinical usefulness of electroanesthesia in man. In the authors' laboratory, more than 2000 applications of electroanesthesia have been given the monkey.

The text consists of the authors' observations on different technics of electroanesthesia and its effects on various physiologic parameters, experiences of electroanesthesia in man, and chapters prepared by investigators in India, Japan, and Russia. While the optimal waveform and currents have not yet been established, it has been shown that various types of diffuse time-changing electric currents applied transcranially via external electrodes can produce unresponsiveness in experimental animals, permitting major surgical procedures without other anesthesia.

The authors have reported much information in a well-organized manner. This book will lead to further investigation and a better understanding of electroanesthesia.

Josef K. Wang, MD
Department of Anesthesiology
Mayo Clinic
Rochester, Minnesota

IN THE NEXT ISSUE

Scientific Articles

July-Aug., 1976

PHYSOSTIGMINE REVERSAL OF SEDATION IN PARTURIENTS—Douglas B. Smith, M.D., Richard B. Clark, M.D., Stacy R. Stephens, M.D., Robert L. Sherman, M.D., and Marshall L. Hyde, M.D., Little Rock, Arkansas.

ON THE HISTORY OF IDEAS IN ANESTHESIA—Leroy D. Vandam, M.D., Boston, Massachusetts.

SPINAL ANESTHESIA FOR LUMBAR DISC SURGERY: REVIEW OF 576 OPERATIONS—David J. Silver, M.D., Rembrandt H. Dunsmore, M.D., and Charles M. Dickson, M.D., Hartford, Connecticut.

FLUROXENE (2,2,2-TRIFLUOROETHYL VINYL ETHER) TOXICITY: A CHEMICAL ASPECT — G. G. Harrison, M.D., F.F.A.R.C.S., K. Ivanetich, Ph.D., L. Kaminsky, Ph.L.D., and M. J. Halsey, D.Phil., University of Cape Town, South Africa and Northwick Park, Harrow, England.

INFLUENCE OF PANCURONIUM ON POTASSIUM EFFLUX PRODUCED BY SUCCINYLCHOLINE—Halappa N. Konchigeri, M.D., and Cheng-Hin Tay, M.D., Chicago, Illinois.

PERIOPERATIVE AWARENESS AND RECALL—Volker Eisele, M.D., Avron Weinreich, M.D., and Stuart Bartle, M.D., New York, New York.

POSTTHORACOTOMY INTERCOSTAL BLOCK: COMPARISON OF ITS EFFECTS ON PULMONARY FUNCTION WITH THOSE OF INTRAMUSCULAR MEPERIDINE—Ronald J. Faust, M.D., and Lee A. Nauss, M.D., Rochester, Minnesota.

SEVERE HYPERTENSION IN A CHILD WITH WILMS' TUMOR: A CASE REPORT—Milton L. Cobb, M.D., and Robert W. Vaughan, M.D., St. Louis, Missouri, and Tuscon, Arizona.

"ACUPUNCTURE ANESTHESIA"—A CLINICAL STUDY—Jerome H. Modell, M.D., Peter K. Y. Lee, M.D., Hal G. Bingham, M.D., Donald M. Greer, Jr., M.D., and Mutaz B. Habal, M.D., Gainesville, Florida.

CLINICAL EVALUATION OF INJECTABLE LORAZEPAM AS A PREMEDICANT: THE EFFECT ON RECALL—Casey D. Blitt, M.D., W. Clayton Petty, M.D., Will A. Wright, M.D., and Barbara Wright, Tucson, Arizona.

SPINAL ANESTHESIA: BUPIVACAINE VERSUS TETRACAINE—A. Eugene Pflug, M.D., Geordis M. Aasheim, M.D., and Harold A. Beck, B.S., Seattle, Washington.

THE LOCAL ANESTHETIC ACTIVITY OF TETRODOTOXIN ALONE AND IN COMBINATION WITH VASOCONSTRICTORS AND LOCAL ANESTHETIC AGENTS—H. Jack Adams, Ph.D., Murray Reid Blair, Jr., Ph.D., and Bertil H. Takman, Ph.D., Worcester, Massachusetts.

RESPIRATORY DISTRESS WITH LEFT AORTIC ARCH, RIGHT DESCENDING AORTA AND RIGHT LIGAMENTUM ARTERIOSUM—S. S. Moorthy, M.B., M.D., Edmund A. Franken, M.D., Alvin M. LoSasso, M.D., and Harold King, M.D., Indianapolis, Indiana.

NEUROMUSCULAR BLOCKING EFFECTS OF AMINOGLYCOSIDE ANTIBIOTICS ON FAST- AND SLOW-CONTRACTING MUSCLES OF THE CAT—H. R. Adams, D.V.M., Ph.D., B. P. Mathew, B.S., R. H. Deske, D.V.M., and H. D. Mercer, D.V.M., Dallas, Texas.

INFLUENCE OF PANCURONIUM OR d-TUBOCURARINE ON CIRCULATORY RESPONSES FOLLOWING ANESTHETIC INDUCTION—Robert K. Stoelting, M.D., Indianapolis, Indiana.

ELECTROANESTHESIA (EA) STUDIES: EA PRODUCED BY STIMULATION OF SENSORY NERVES OF THE SCALP IN RHESUS MONKEYS—Robert H. Smith, M.D., San Francisco, California.

CHANGES IN BLOOD CHEMISTRIES FOLLOWING PROLONGED ENFLURANE ANESTHESIA—E. I. Eger II, M.D., R. K. Calverley, M.D., and N. Ty Smith, San Francisco, California.

CARDIOVASCULAR AND RESPIRATORY EFFECTS OF ISOPROTERENOL BEFORE AND AFTER ARTIFICIAL HEART IMPLANTATION—Wen-Shin Liu, M.D., Theodore H. Stanley, M.D., Jesus Isern-Amaral, M.D., Bruce Ward, Ph.D., Salt Lake City, Utah.

THOUGHTS ABOUT MEDICAL WRITING. XXXVI—Charles G. Roland, M.D., Rochester, Minnesota.

HYPOXEMIA FOLLOWING INTERMITTENT POSITIVE PRESSURE BREATHING THERAPY—Fred G. Wright, Jr., Captain, USAF, MC, Mary F. Foley, LT. COL., USAF, (Res.), John B. Downs, M.D., and Michael R. Hodges, SSGT, USAF, MC, Lackland Air Force Base, Texas.

INTRAOPERATIVE AWAKENING FOR PREVENTION OF NEUROLOGICAL SEQUELAE FOLLOWING HARRINGTON ROD SPINE FUSION—K. G. Sudhir, F.F.A.R.C.S., Robert M. Smith, M.D., John E. Hall, M.D., Dolly D. Hansen, M.D., and Dean Crocker, M.D., Boston, Massachusetts.

CASE HISTORY #91 —SUSTAINED HIGH INSPIRED OXYGEN TENSIONS WITHOUT TOXIC SEQUELAE—Philip S. Gibbs, M.D., S. S. Moorthy, M.D., Alvin M. LoSasso, M.D., Indianapolis, Indiana.

BRIEF REPORTS:

SIGNIFICANCE OF PCO_2 WITHIN LOW PRESSURE ENDOTRACHEAL TUBE CUFFS—Paul R. Levesque, M.D., Boston, Massachusetts.

SHEARING HAZARDS OF INTRA-ARTERIAL TEFLON CATHETERS—Edward A. Talmage, M.D., Sayre, Pennsylvania.

MODIFICATION OF A BIRD® MARK-14 ANESTHESIA VENTILATOR FOR GREATER VERSATILITY—C. S. Jones, M.B., Ch.B., Worcester, South Africa.

ESTIMATION OF ANESTHETIC SOLUBILITY IN BLOOD—Alfred Feingold, M.D., Miami, Florida.

TEMPERATURE CONTROL IN THE NEWBORN PERIOD—Michael B. Meyers, M.D., and Tae H. Oh., M.D., New Haven, Connecticut.

ACUTE ETHANOL INTOXICATION AND ITS PROLONGED EFFECT ON A FULL-TERM NEONATE—S. S. Kim, M.D., and Robert Hodgkinson, M.D., Bronx, New York.

PNEUMATOCELE OF THE LARYNX: A COMPLICATION OF PERCUTANEOUS TRANSTRACHEAL VENTILATION—Edward Carden, M.B., FRCP(C), and Thomas C. Calcaterra, M.D., Los Angeles, California.

EVALUATION OF LARYNX AND TRACHEA BY XERORADIOGRAPHY—S. S. Moorthy, M.B., B.S., Alvin M. LoSasso, M.D., Harold King, M.D., and Edmund Franken, M.D., Indianapolis, Indiana.

A Guide for Authors

Anesthesia and Analgesia . . . Current Researches invites original manuscripts on subjects pertinent to the specialty of anesthesiology. Original articles accepted for publication, or papers presented at the Society's annual scientific meetings which subsequently may be published in the Journal, become the property of the International Anesthesia Research Society. Reproduction in whole or in part is not permitted except by written consent of the publisher and the author.

Submit manuscripts in triplicate to—
T. H. Seldon, M.D., Editor
Kahler East, Suite C
Rochester, Minnesota 55901, U.S.A.

All papers are reviewed by the Editorial Board and other selected referees. If accepted for publication, editorial revisions may be made to aid clarity and understanding without altering the meaning. Edited copy is submitted to authors for approval before it is sent to the printer. Page proof will be submitted to authors for final approval. Reprint order forms will accompany page proof.

Titles should be concise but informative, with thought given to the use of key words for indexing. Ninety characters, including punctuation and spaces, should be sufficient.

Coauthors' names should be followed by the major degree, professional affiliation, and address.

Abstract: On the first page of manuscript, an abstract of from 50 to 250 words, according to length of article, but not exceeding one double-spaced typed page, should describe purpose, methods, results, and conclusions, as succinctly as possible. This replaces both former Capsule Review and Summary, but is the same in content and format.

Type manuscript (in triplicate) on 8½ x 11-inch white paper, with 1½ inch margins at top, bottom, and both sides. Double space ALL typing, including references, legends and footnotes.

References: About 20 references are acceptable. In extensive reviews of the literature, readers will be advised that longer reference citations can be obtained from author. Citations should include (1) last name of author followed by initials without internal punctuation; (2) commas separate names and initials of authors; (3) four or more authors are designated as "et al;" (4) journal name is abbreviated according to Index Medicus style; (5) references from books show (a) city of publication, name of publisher, date of publication, after book title; (6) journal references give volume, first and last page numbers, year. (See previous issues of *Anesth & Analg* for style.)

Tables should be self-explanatory and should supplement, not duplicate, the text.

Photographs should have sharp contrast, be on *glossy* paper unmounted, and 4 by 5 inches or larger. *Polaroid prints damage easily in handling and thus may reproduce indistinctly. Glossy prints are preferred.* Submit photographs of roentgenograms with contrasts as in original and sharply defined; "TOP" must be identified. All illustrative materials, charts, etc., must be submitted in triplicate, clearly numbered according to text and legend.

Lettering on charts and graphs must be large enough to be legible when reduced in size. Curves, scatter dots, etc., should contrast with reference lines.

Drawings must be in black (India) ink on white background and should be of professional quality.

Legends for illustrations should be concise and typed on one page. Legends for photomicrographs should show stain and magnification data.

Drug names used in the text should be generic unless trade names are essential to the discussion.

Multiple Publication: To avoid violating existing copyrights, a statement should accompany each submitted article indicating that the material in question:

1. Has not been simultaneously submitted to another journal.
2. Has not been previously published elsewhere.

a. Abstracts of 400 words or less do not constitute prior publication.

b. A report issued by requirement of a governmental agency or comparable granting institution does not constitute prior publication.

c. Extracting by news media does not constitute prior publication unless all vital tables and pertinent conclusions are involved or unless such publication was actively solicited by the authors.

Legal considerations require letters of permission from authors and publishers for use of illustrations or quotations originally appearing elsewhere, and also written permission for use of photographs of identifiable patients. Identifying information, such as names, initials, hospital numbers, and dates, must be avoided.

When experimentation involving human subjects is reported, an appropriate statement regarding informed consent should be made.

Case reports should include only significant data. Laboratory findings should be restricted to those pertinent to the discussion.

Symbols used for respiratory physiology should follow Fed. Proc. 9:602, 1950.

Explanation of abbreviations and symbols used within the text should be added as a footnote.

Example: torr: Unit of pressure of 1 mm. of mercury at 0° C. and standard gravity.

CHECK LIST

- ☐ Title
- ☐ Authors
- ☐ Abstract
- ☐ Text
- ☐ Tables
- ☐ References
- ☐ Figures
- ☐ Legends

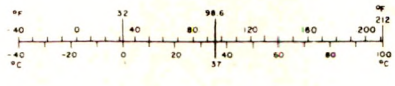
Manuscripts and all illustrations should be mailed flat, *in triplicate,* with cardboard protection. The author should retain one complete copy, including tables and illustrations.

Metric Conversions

HEIGHT			WEIGHT	
Cm	Feet	Inches (approx.)	Kilograms	Pounds
15	0 ft.	6 in.	1	2.2
30	1 ft.	0 in.	5	11
45	1 ft.	8 in.	10	22
60	1 ft.	11½ in.	15	33
75	2 ft.	5½ in.	20	44
105	3 ft.	5 in.	25	55
115	3 ft.	9 in.	30	66
120	3 ft.	11 in.	35	77
125	4 ft.	1 in.	40	88
130	4 ft.	3 in.	45	99
135	4 ft.	5 in.	50	110
140	4 ft.	7 in.	55	121
145	4 ft.	9 in.	60	132
150	4 ft.	11 in.	65	143
155	5 ft.	1 in.	70	154
160	5 ft.	3 in.	75	165
165	5 ft.	5 in.	80	176
170	5 ft.	7 in.	85	187
175	5 ft.	9 in.	90	198
180	5 ft.	11 in.	95	209
185	6 ft.	1 in.	100	220
190	6 ft.	3 in.	105	231
195	6 ft.	5 in.	110	242
200	6 ft.	7 in.	115	253
205	6 ft.	9 in.	120	264
210	6 ft.	11 in.	125	275
215	7 ft.	1 in.		

APPROXIMATE CONVERSIONS FROM METRIC MEASURES

Symbol	When You Know	Multiply by	To Find	Symbol
	LENGTH			
mm	millimeters	0.04	inches	in
cm	centimeters	0.4	inches	in
m	meters	3.3	feet	ft
m	meters	1.1	yards	yd
km	kilometers	0.6	miles	mi
Symbol	When You Know	Multiply by	To Find	Symbol
	MASS (weight)			
g	grams	0.035	ounces	oz
kg	kilograms	2.2	pounds	lb
t	tonnes (1000 kg.)	1.1	short tons	
Symbol	When You Know	Multiply by	To Find	Symbol
	TEMPERATURE (exact)			
°F	Fahrenheit temperature	5/9 (after subtracting 32)	Celsius temperature	°C



Anesthesia and Analgesia CURRENT RESEARCHES

BACK ISSUES AVAILABLE

Available at $3.00 Per Issue

Vol.	Year	Numbers Available						Vol.	Year	Numbers Available					
33	1954	–	2	3	4	5	6	41	1962	–	2	3	–	5	6
34	1955	1	–	3	4	5	6	42	1963	–	–	3	4	5	6
35	1956	1	2	3	–	–	6	43	1964	–	2	–	–	–	6
36	1957	–	–	–	–	–	6	44	1965	–	2	3	4	5	6
37	1958	1	2	3	4	5	6	45	1966	–	2	–	–	–	6
38	1959	–	2	3	4	–	6	46	1967	–	–	3	–	–	6
39	1960	–	–	3	4	5	6	47	1968	–	–	3	4	5	6
40	1961	–	–	3	4	5	6	48	1969	1	2	3	–	5	–

Available at $4.50 Per Issue

Vol.	Year	Numbers Available						Vol.	Year	Numbers Available					
49	1970	1	–	–	–	5	6	53	1974	–	2	3	4	–	6
50	1971	1	2	3	–	–	–	54	1975	1	2	–	–	–	6
51	1972	–	2	3	–	5	6	55	1976	1	2				
52	1973	1	2	3	4	–	–								

SINGLE ISSUES PRIOR TO 1954: Write to publisher at address below for listing of issues available at $2.00 each.

BOUND VOLUMES AVAILABLE: $8.00—For Years 1947, 1948, 1949; $10.00—For Years 1953, 1955

OTHER PUBLICATIONS AVAILABLE:

"Basic and Clinical Physiology of the Liver" (Supplement to Sept.-Oct. 1965 issue)—$3.00.

Ten-Year (1960-1969) Cumulative Index—$3.00.

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, Ohio 44122

Please send me the publications circled above, or listed hereunder:

☐ Check for $_____ enclosed.

☐ Please send bill with understanding that ordered material will be sent when payment is received.

Name_____

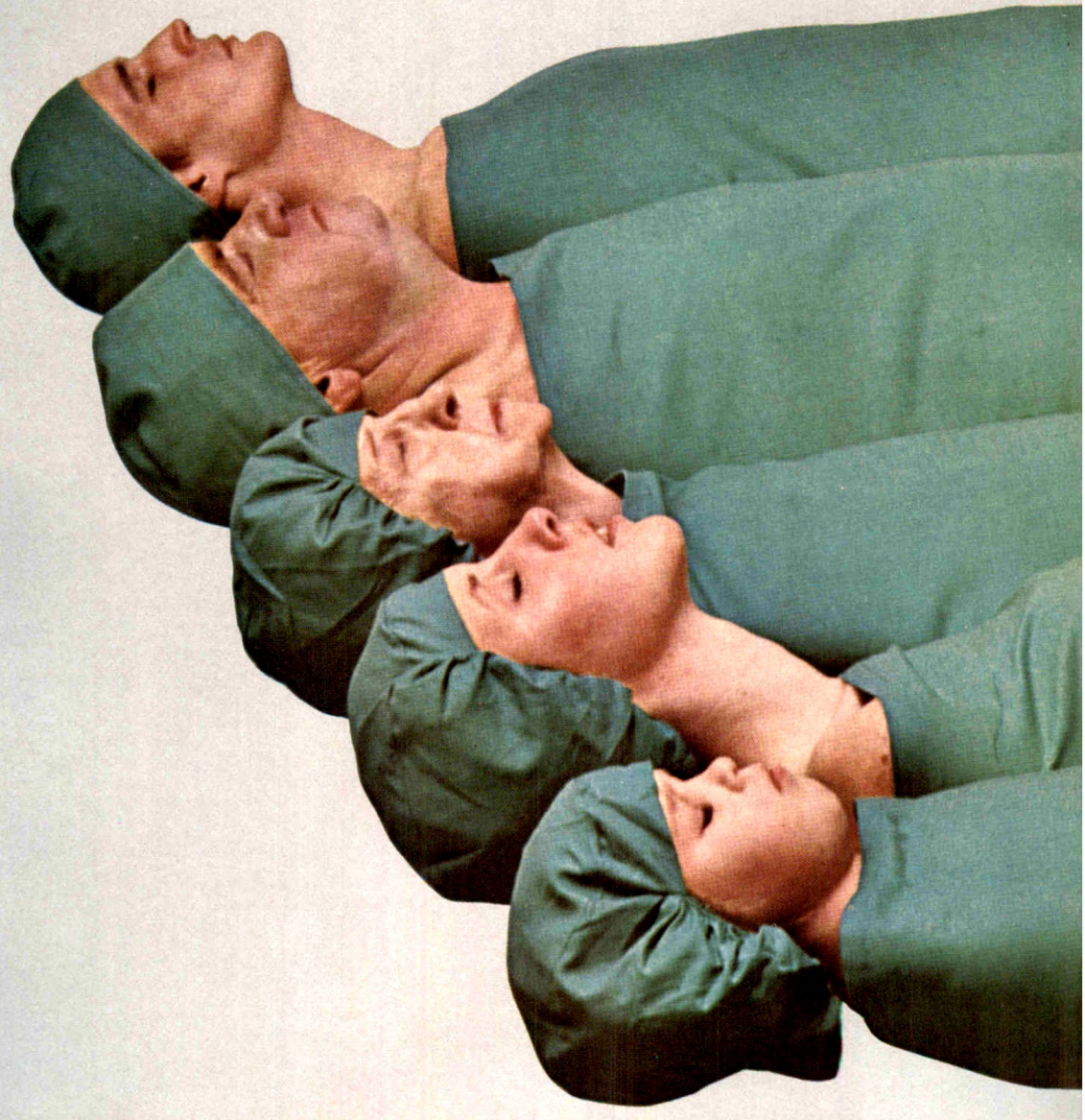
Address_____

City, State, Zip_____

Clinically proven
nondepolarizing muscle relaxant

PAVULON®
pancuronium bromide

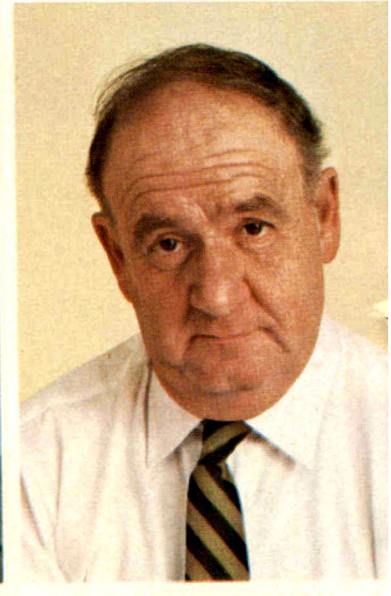
for many patients
for many reasons



Please turn page for full prescribing information

An unusually fast-acting nondepolarizing blocking agent [1-5]

PAVULON®
pancuronium bromide



for many patients for many reasons

in pediatric surgery[6-12]

Pavulon® has been used with satisfactory results in pediatric patients undergoing elective surgery[11], abdominal surgery[7] and cardiovascular surgery[8]. Dose response studies indicate that, except for neonates, dosage is the same as for adults. In neonates, a test dose of 0.02 mg/kg is recommended to determine responsiveness.

in geriatric surgery[13]

Pavulon® can be considered a preferred relaxant for major surgical procedures in the aged patient because of the relative absence of significant side effects.

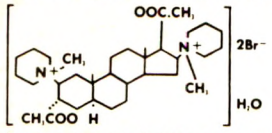
in the high risk patient[2-5, 14-18]

Pavulon® is often preferred for poor risk patients[5,14,16] especially those with asthma or chronic bronchitis[2,14,16,17], cardiovascular disease[4,5,16,18] and patients undergoing abdominal, thoracic or other major surgery[2,5], including open heart surgery[15]. Caution should be exercised, however, in the presence of renal disease since a major portion of the administered drug is excreted unchanged in the urine.

PAVULON® (pancuronium bromide)

THIS DRUG SHOULD ONLY BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: Pavulon (pancuronium bromide) is the aminosteroid 2 beta, 16 beta-dipiperidine-5 alpha-androstane-3 alpha, 17 beta-diol diacetate dimethobromide. It has the following structural formula:



ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon is approximately 5 times as potent as d-tubocurarine chloride.

The onset and duration of action of Pavulon is dose dependent. With the administration of 0.04 mg. per kg. the onset of action, as measured by a peripheral nerve stimulator, is usually within 45 seconds, and its peak effect is usually within 4½ minutes; recovery to 90% of control twitch height usually takes place in less than one hour. Larger doses, more suitable for endotracheal intubation, such as 0.08 mg. per kg. of Pavulon have an onset of action of about 30 seconds, and a peak effect within 3 minutes. Supplemental incremental doses of Pavulon, following the initial dose, slightly increase the magnitude of blockade, and significantly increase the duration of the blockade.

Pavulon has little effect upon the circulatory system. The most frequently reported observation is a slight rise in pulse rate.

Human histamine assays, and clinical observations, as well as in *vivo* guinea pig testing, and in *vitro* mast cell testing, indicate that histamine release rarely, if ever, occurs.

Pavulon is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, kanamycin, and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

Pavulon has no known effect on consciousness, the pain threshold, or cerebration.

INDICATIONS: Pavulon is indicated as an adjunct to anesthesia to induce skeletal muscle relaxation. It may also be employed to facilitate the management of patients undergoing mechanical ventilation.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards. There are insufficient data to support safe use of Pavulon in obstetrics, so such use is not recommended.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: The most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane, and methoxyflurane. No increase in intensity of blockade or duration of action of Pavulon is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. The dosage information which follows has been derived from dose-response studies based on body weight and is intended to serve as a guide only. Since potent inhalational agents or prior administration of succinylcholine enhance the intensity of blockade and duration of Pavulon (see DRUG INTERACTION), these factors should be taken into consideration in selection of initial and incremental dosage.

In adults the initial intravenous dosage range is 0.04 to 0.1 mg. per kg. Later incremental doses starting at 0.01 mg. per kg. may be used. These increments slightly increase the magnitude of the blockade, and significantly increase the duration of blockade, because a significant number of myoneural junctions are still blocked when there is clinical need for more drug.

If Pavulon is used to provide skeletal muscle relaxation for endotracheal intubation, doses of 0.06 to 0.1 mg. per kg. are recommended. Conditions satisfactory for intubation are usually present within 2 to 3 minutes. The ability of the anesthetist to intubate with Pavulon (pancuronium bromide) improves with experience.

Dosage in Children; Dose-response studies in children indicate that, with the exception of neonates, dosage requirements are the same as for adults. Neonates are especially sensitive to non-depolarizing neuromuscular blocking agents, such as Pavulon, during the first month of life. It is recommended that a test dose of 0.02 mg. per kg. be given first in this group to measure responsiveness.

MANAGEMENT OF PROLONGED NEUROMUSCULAR BLOCKADE: Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Pavulon as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade. Under such circumstances the primary treatment is manual or mechanical ventilation and maintenance of a patent airway until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) or neostigmine, in conjunction with atropine, will usually antagonize the skeletal muscle relaxant action of Pavulon. These should be accompanied by or preceded by injection of atropine sulfate to minimize the incidence of cholinergic side effects, notably excessive secretions and bradycardia. Satisfactory reversal can be judged by adequacy of skeletal muscle tone, and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and adjuncts which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade; ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference to the specific package insert of the reversal agents should be made.

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED:

2 ml. ampuls—2 mg./ml.—box of 25
5 ml. ampuls—2 mg./ml.—box of 25
10 ml. multiple dose vials—1 mg./ml.—box of 25

References:

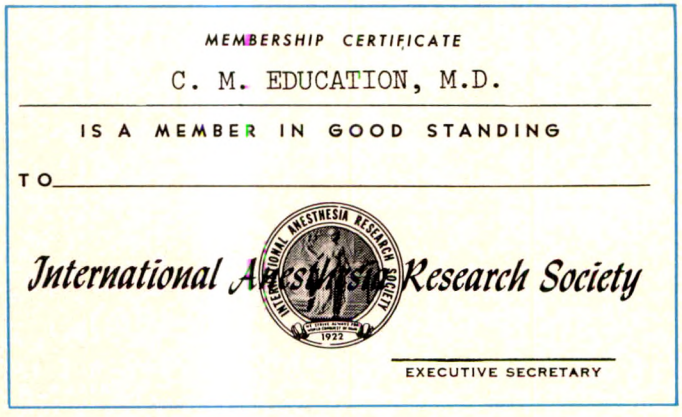
1. Baird, W. L. M. and Reid, A. M.: Brit. J. Anaesth. *39*:775, 1967.
2. McDowell, S.A. and Clarke, R.S.J.: Anaesthesia *24*:581, 1969.
3. Katz, R. L.: Anesthesiology *34*:550, 1971.
4. McIntyre, J. W. R. and Gain, E. A.: Anesth. and Analg. *50*:813, 1971.
5. Dobkin, A.B., *et al.*: Canad. Anaesth. Soc. J.: *18*:512, 1971.
6. Nightingale, D. A. and Bush, G. H.: Brit. J. Anaesth. *45*:63, 1973.
7. Goudsouzian, N. C., Ryan, J. F., and Savarese, J. J.: Anesth. *41*:95, 1974.
8. Bennett, E. J., Dalal, F. Y., and Fisher, M.: M. E. J. Anaesth. *3*:413, 1972.
9. Yamamoto, T., Baba, H., and Shiratsuchi, T.: Anesth. and Analg. *51*:919, 1972.
10. Bennett, E. J., Bowyer, D. E., Giesecke, Jr., A. H., and Stephen, C. R.: Anesth. and Analg. *52*:12, 1973.
11. Lippmann, M. and Rogoff, R. C.: Anesth. and Analg. *53*:684, 1974.
12. Bennett, E. J., Daughety, M. J., Bowyer, D. E., and Stephen, C. R.: Anesth. and Analg. *50*:798, 1971.
13. Lorhan, P. H. and Lippmann, M.: Anesth. and Analg. *51*:914, 1972
14. Fastner, Z. and Agoston, S.: Clinical Trials J. 7:254, 1970.
15. Sellick, B. A.: Der Anaesthesist *20*:76, 1971.
16. Baird, W. L. M.: Irish J. Med. Sc. (7th Series) *1*:559, 1968.
17. Nana, A., Cardan, E., and Leitersdorfer, T.: Anaesthesia *27*:154, 1972.
18. Levin, N. and Dillon, J.B.: Anesth. and Analg. *50*:808, 1971.

Organon

Organon Inc.
West Orange, N. J. 07052

I. A. R. S. MEMBERSHIP

For Your In-training and Continuing Medical Education


MEMBERSHIP CERTIFICATE

C. M. EDUCATION, M.D.

IS A MEMBER IN GOOD STANDING

TO

International Anesthesia Research Society

EXECUTIVE SECRETARY

The International Anesthesia Research Society is a non-profit, scientific and educational corporation of the State of Ohio founded in 1922 "To Foster Progress and Research in Anesthesia." To this end it performs two functions: (1) It publishes a bi-monthly journal, "ANESTHESIA and ANALGESIA . . . Current Researches"; and (2) It sponsors an annual scientific "Congress" meeting which meets the criteria for Category 1 credit toward the AMA Physicians Recognition Award.

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state or national anesthesia organization.

MEMBERSHIP - ASSOCIATE MEMBERSHIP

MEMBERSHIP is open to individuals with doctorate degrees, licensed to practice in the medical, dental, osteopathic or veterinary medicine professions (i.e., MD, MB, DDS, DMD, DO, DMV); and to individuals with doctorate degrees (Ph.D.) in any scientific discipline, engaged in academic, private or commercial research.

ASSOCIATE MEMBERSHIP is open to individuals in the allied health professions, duly certified by their professional accrediting organization as nurse anesthetists (CRNA), physician assistants-anesthesia (PA-Anesth.), inhalation therapists (ARIT) or respiratory technicians (CRTT).

DUES are $25 per year for Members and Associate Members, and include a subscription to ANESTHESIA and ANALGESIA . . . Current Researches. Members are also entitled to reduced registration fee at IARS annual scientific meetings.

EDUCATIONAL MEMBERSHIP

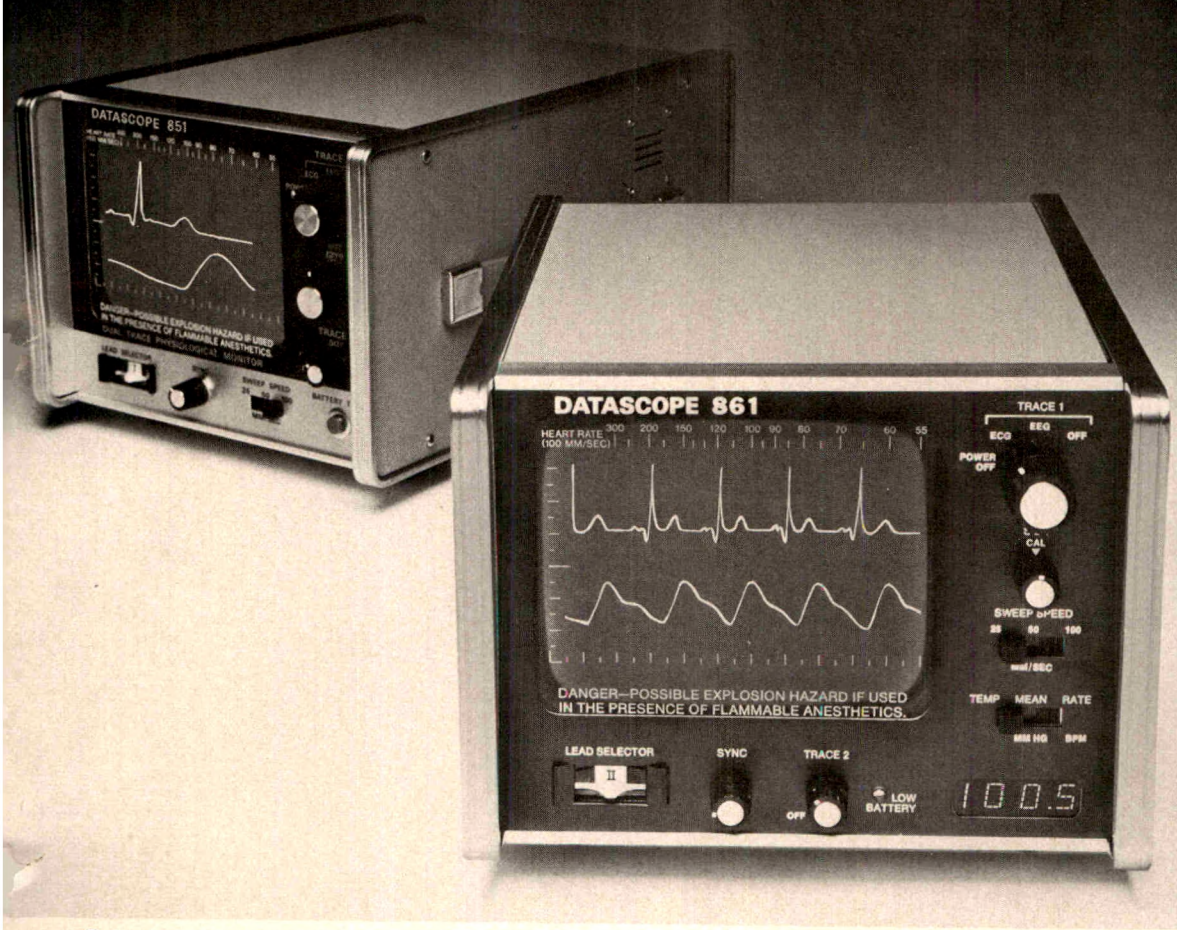
EDUCATIONAL MEMBERSHIP is open to interns and residents in anesthesiology training programs; registered nurses enrolled in nurse anesthesia schools; students in inhalation or respiratory therapy training programs, or in physician assistant anesthesia programs.

The official Educational Membership application blank must be completed by the individual applicant, and signed by his or her training program director.

Dues are $25 for a single, two-year period during the member's anesthesia training period, and include a two-year subscription to ANESTHESIA and ANALGESIA . . . Current Researches. Educational Members are entitled to complimentary registration at IARS annual scientific meetings.

Application forms are available from Cleveland business office. Program Directors are invited to obtain a supply of Educational Membership applications for their students in training.

THE MOST POPULAR MONITORS MADE. MADE EVEN BETTER.



For some time now, our monitors have been selected for use in surgery by more medical people than any other battery-powered monitors in the world. Because we give you more of what you want in a monitor than any other monitors in the world.

However, this didn't stop us from improving them.

Our new Datascope 851 and 861 will now give you heart rate not only from ECG, but also from pulse or blood pressure.

And both monitors will give you 2 traces. So you can monitor ECG (or EEG) and pulse simultaneously.

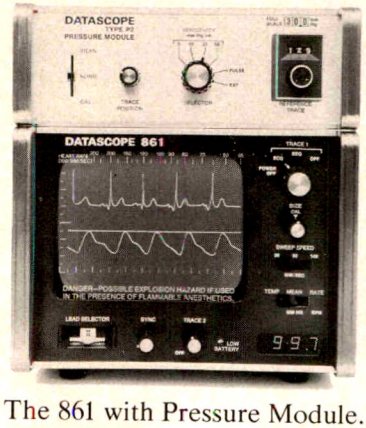
And both give you beat by beat synchronization†. So a single ECG complex shows up with each full sweep.

The 861 does even more. It monitors body temperature. On a digital read-out. And this same digital display will give you heart rate when you want it; or mean blood pressure when you are using the 861 with our Pressure Module.

For all the things our 851 and 861 do, they're surprisingly portable. And they offer longer battery-operating time than any other monitors. In some cases, actually twice as long.

Will they continue to be the most popular monitors made? More so.

For further information about our new 851, 861, or our Pressure Module, write Datascope Corp., 580 Winters Ave., Paramus, NJ 07652.



The 861 with Pressure Module.

THE DATASCOPE 851/861

†U.S. PATENT NO. 3457452

take the **Excessive Anxiety** out of **Anesthesi**

Vistaril I.M. (hydroxyzine HCl) helps allay the anxiety that may complicate premedication, induction and recovery room emergence.

It has no significant depressant effects on respiratory or circulatory function and often reduces postoperative emesis.

Vital signs are seldom impaired. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.

And, because it may enhance the effect of injectable analgesics, requirements of narcotic and nonnarcotic analgesics, such as meperidine, morphine sulfate and pentazocine, may be reduced.

Vistaril I.M. is physically compatible with most commonly used analgesics, and can be mixed with them in the same syringe.

Alone, or as an adjunct for use with injectable analgesics, the maximum recommended dosage of Vistaril I.M. is 100 mg. While the analgesic dosage needed will usually be reduced, the actual dosage of Vistaril I.M. should be titrated against the individual patient's clinical response.

Vistaril® I.M.
(hydroxyzine HCl)
100 mg./2 ml., 50 mg./ml. and 25 mg./ml. Vials and Isojects®

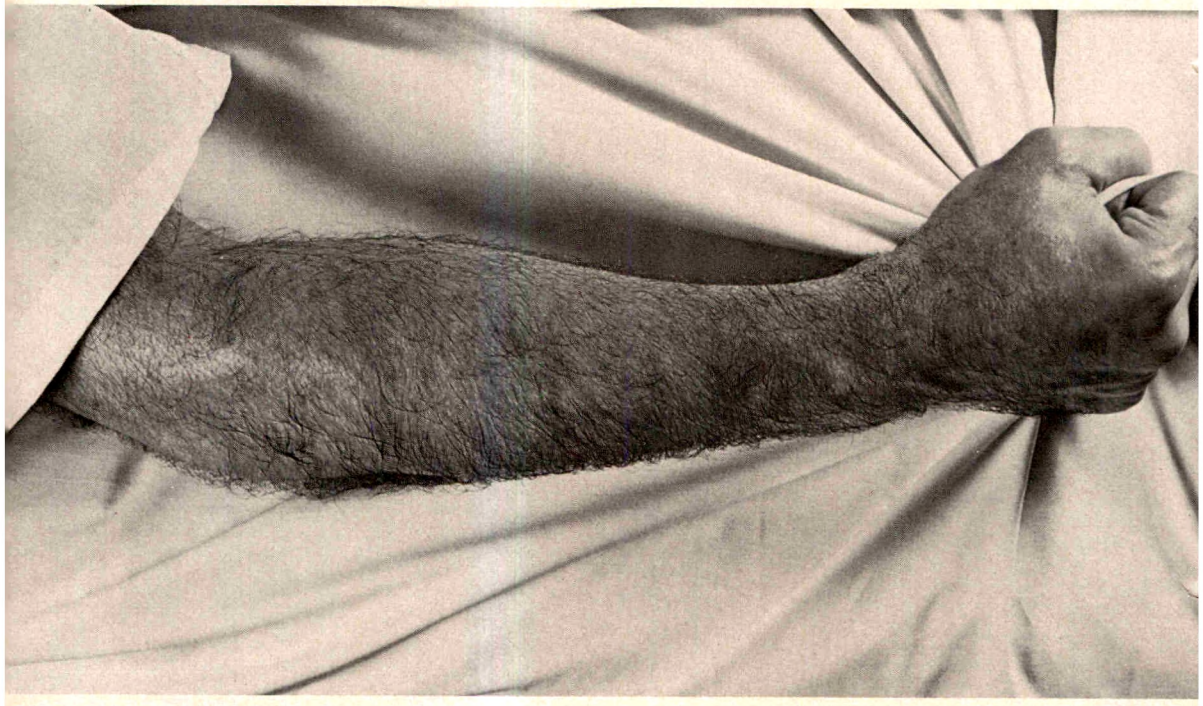
Pfizer
LABORATORIES DIVISION
PFIZER INC.

Please see Brief Summary on following page for contraindications, precautions and adverse reactions.

Vistaril® I.M.
(hydroxyzine HCl)

100 mg./2 ml., 50 mg./ml. and 25 mg./ml.
Vials and Isojects®

Calm Before Anesthesia... In Recovery



Brief Summary
VISTARIL® (hydroxyzine hydrochloride) Intramuscular Solution
For Intramuscular Use Only

Contraindications: Hypersensitivity to hydroxyzine. The solution for intramuscular use *must not* be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate. Until adequate data are available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: *Hydroxyzine may potentiate the action of central nervous system depressants such as narcotics and barbiturates.* In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscle of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in c to minimize the possibility of damage to the sciatic nerve. The deltoic area should be used only if well developed, such as in certain adults older children, and only with caution to avoid radial nerve injury. Injections should not be mac'e in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid intravascular inject

Adverse Reactions: Drowsiness may occur; if so, it is usually transit and may disappear in a few days of continued therapy or upon dosa reduction. Dryness of the mouth may occur with higher doses. Involu tary motor activity, including rare instances of tremor and convulsion has been reported, usually with higher than recommended dosage.

Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg./m 10 ml. vial; 50 mg./ml.—2 ml. and 10 ml. vial; Isoject®, 25 mg./ml. ar 50 mg./ml., 1 ml. fill; 100 mg./2 ml., 2 ml. fill.
Military Depot: NSN 6505-00-052-1367 (50 mg./ml., 10 ml. vial)
VA Depot: NSN 6505-00-052-1367B (50 mg./ml., 10 ml. vial)

More detailed professional information available on request.

Pfizer **LABORATORIES DIVISION**
PFIZER INC.

When you need to know

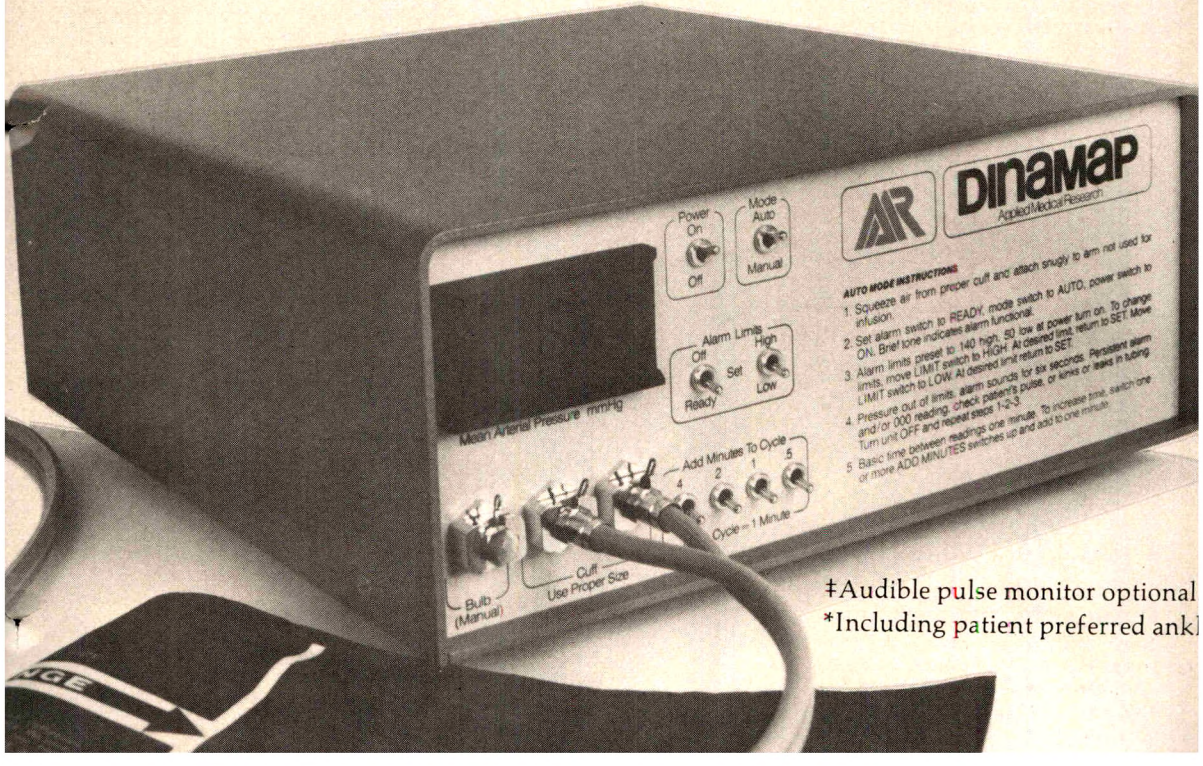
DINAMAP for **non-invasive,** routine monitoring of arterial pressure.‡

Using: An ordinary pressure cuff with no transducer. Easily attached to any limb.*

Provides: Automatic determination and digital display of mean arterial pressure.

Write or call for your demonstration.

Applied Medical Research
6 Columbia Drive
Tampa, Fla. 33606
(813) 251-8390 Dept. 3



‡Audible pulse monitor optional

*Including patient preferred ank

CLASSIFIED ADVERTISING

ANESTHESIOLOGIST — markedly expanding academic medical center located in attractive Midwestern setting requires additional senior and junior faculty; Board certification and teaching experience necessary; salary from $45,000-$75,000 with extraordinary fringe benefit program. Inquiries with curriculum vitae to Box 5-76-B in care of I.A.R.S.

ANESTHESIOLOGIST: Board certified/eligible to join newly formed group of anesthesiologists and nurse anesthetists in New Orleans. Fee for service private practice at 650-bed general hospital and newly opened Pediatric hospital. Write or call Metropolitan Anesthesia Associates, 4520 Melpomene, New Orleans, La. 70185. (504) 822-9331.

ANESTHESIOLOGIST—to join staff in new 400+ bed university affiliated teaching hospital in large metropolitan area. Candidates must be licensed or eligible for licensure in the state of Minnesota at the time they are accepted for employment. Salary commensurate with experience. For further information contact:

Irving Greenfield, Chief of Service
Dept. of Anesthesia
Hennepin County Medical Center
5th and Portland
Minneapolis, MN 55415

ADMINISTRATIVE-TEACHING POSITION WANTED: CRNA with seven years clinical, teaching and administrative experience, plus masters degree. Prefer teaching hospital and authority equivalent to responsibility. Salary important, not hours. For resumé contact: Box 3-76-C in care of I.A.R.S.

ANESTHESIOLOGIST—Position available for Board Certified or eligible Anesthesiologist in an ambulatory surgical facility. Competitive salary with liberal fringe benefits offered. For details, please call D. L. Henderson, M.D., at 318-233-5025, or send vitae to Surgery Center, Inc., 1101 South College Road, Suite 100, Lafayette, Louisiana 70501.

FACULTY POSITIONS

Department of Anesthesiology, Charity Hospital, New Orleans, affiliated with LSU and Tulane Medical Schools, has three faculty positions open for board certified/eligible anesthesiologists at Associate-Assistant Professor, Instructor levels. Duties involve teaching, research, clinical supervision. Salaries negotiable. Send inquiries and curriculum vitae to: M. Naraghi, M.D., Director, Department of Anesthesiology, Charity Hospital, New Orleans, Louisiana 70140.

PEDIATRIC ANESTHESIOLOGY RESIDENCY

Childrens Hospital of Los Angeles

Three-phase program: Clinical, Academic, Investigative, emphasizing practical aspects of anesthesiology related to infants and children.

AMA approval for third-year residency. Positions available from two months to one year.

Apply: George B. Lewis, Jr., M.D.
Head, Division of Anesthesiology
Childrens Hospital of Los Angeles
4650 Sunset Boulevard
Los Angeles, California 90054
Phone (213) 660-2450, Ext. 2262

POSITION WANTED BY CRNA: Experience and masters degree. Seeks position as director of nurse anesthesia school or division. Resumé on request. Reply: Box 3-76-D in care of I.A.R.S.

FACULTY POSITIONS

Department of Anesthesiology, University of Louisville School of Medicine, has faculty positions open for board certified/eligible anesthesiologists. One position reserved for those with special interest in obstetrical anesthesia; work involves teaching, research and/or coordination of clinical activities. Send inquiries and curriculum vitae to K. P. Geevarghese, M.D., P.O. Box 1055, Louisville, Kentucky 40201. An equal opportunity, affirmative action employer.

Young bd. elig. married with no military obligation. 3 year major university training including faculty experience. Particularly qualified in regional anesthesia. Can share cardiac and respiratory consults. Excellent references. Desires Western U.S. Write Box 5-76-A in care of I.A.R.S.

NEBRASKA Opportunity for Anesthesiologist in 450-bed acute care, teaching hospital affiliated with two medical schools; must be board certified or eligible, salary commensurate with education and experience. An equal opportunity employer. Contact J. J. Matoole, M.D., Chief of Staff, Veterans Administration Hospital, 4101 Woolworth Avenue, Omaha, Nebraska 68105. (402) 346-8800, Ext. 442.

ANESTHESIOLOGIST, FFARCS, age 31, 6½ years experience in England and Holland, ECFMG and US Immigration visa; seeks challenging position academic or multispecialty clinic. Contact: V. S. Joshi, 2 Castelmorelaan, Maastricht, Holland.

Rates for classified advertising are $3.00 per line, minimum 5 lines. Box number ads $3.50 per line. Classified Display rates on request. Copy deadline 6 weeks prior to publication. Do not submit payment with order; invoices will be sent for payment prior to publication. Ad copy, subject to acceptance by publisher, should be mailed to: Anesthesia and Analgesia . . . Current Researches, 3645 Warrensville Center Rd., Cleveland, Ohio 44122.

A mainstay of modern anesthesia

- As an adjunct to general anesthesia
- As a supplement to regional anesthesia
- Used without a general anesthetic in certain diagnostic procedures

INNOVAR® injection is available for use only upon direction of a physician.

Special educational material available

A Programmed Instruction Manual on the chemistry, pharmacology and clinical applications of INNOVAR injection and its components is available from McNeil Laboratories. For further information, please write: Product Director, INNOVAR injection, McNeil Laboratories, Inc., Fort Washington, Pa. 19034.

© McN 1975

For prescribing information including Contraindications, Warnings, Precautions and Adverse Reactions, please turn page.

Innovar® injection

The two components of INNOVAR® injection, fentanyl and droperidol, have different pharmacologic actions. Before administering INNOVAR injection, the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action.

DESCRIPTION

Each cc. contains (in a 1:50 ratio):

Fentanyl ..... 0.05 mg.
as the citrate

Warning: May be habit forming

Droperidol ..... 2.5 mg.
Lactic acid for adjustment of pH to 3.5± 0.3

FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY

Protect from Light

ACTIONS INNOVAR injection is a combination drug containing a narcotic analgesic, fentanyl, and a neuroleptic (major tranquilizer), droperidol. The combined effect, sometimes referred to as neuroleptanalgesia, is characterized by general quiescence, reduced motor activity, and profound analgesia; complete loss of consciousness usually does not occur from use of INNOVAR injection alone. The incidence of early postoperative pain and emesis may be reduced.

A. Fentanyl is a narcotic analgesic with actions qualitatively similar to those of morphine and meperidine. Fentanyl in a dose of 0.1 mg. (2.0 cc.) is approximately equivalent in analgesic activity to 10 mg. of morphine or 75 mg. of meperidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. Fentanyl appears to have less emetic activity than other narcotic analgesics. Histamine assays, and skin wheal testing in man, as well as *in vivo* testing in dogs indicate that histamine release rarely occurs with fentanyl.

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. It may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia, and bronchoconstriction.

The onset of action of fentanyl is almost immediate when the drug is given intravenously; however, maximal analgesic and respiratory depressant effect may not be noted for several minutes. The average duration of action of the analgesic effect is 30 to 60 minutes. Following intramuscular administration, the onset of action is from seven to eight minutes, and the duration of action is from one to two hours. Although the duration of the respiratory depressant effect is unknown, as with other narcotic analgesics, it may be considerably longer than the analgesic effect.

B. Droperidol produces marked tranquilization and sedation. It also produces an antiemetic effect as evidenced by the antagonism of apomorphine in dogs. It potentiates other CNS depressants. It also produces mild alpha adrenergic blockade, peripheral vascular dilatation and reduction of the pressor effect of epinephrine. Droperidol can produce hypotension and decreased peripheral vascular resistance. It may decrease pulmonary arterial pressure (particularly if it is abnormally high). It may reduce the incidence of epinephrine-induced arrhythmias but it does not prevent other cardiac arrhythmias. The onset of action is from three to ten minutes following intravenous or intramuscular administration. The full effect, however, may not be apparent for 30 minutes. The duration of the sedative and tranquilizing effects generally is two to four hours. Alteration of consciousness may persist as long as 12 hours. This is in contrast to the much shorter duration of action of fentanyl.

INDICATIONS INNOVAR injection is indicated to produce tranquilization and analgesia for surgical and diagnostic procedures. It may be used as an anesthetic premedication, for the induction of anesthesia, and as an adjunct in the maintenance of general and regional anesthesia. If the supplementation of analgesia is necessary, SUBLIMAZE® (fentanyl) injection alone rather than the combination drug INNOVAR injection should usually be used.

CONTRAINDICATIONS INNOVAR injection should not be used in patients who are hypersensitive to either component.

WARNINGS PATIENTS WHO HAVE RECEIVED *INNOVAR* INJECTION SHOULD BE UNDER APPROPRIATE SURVEILLANCE.

RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INNOVAR injection, the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses, as low as 1/4 to 1/3 those usually recommended.

INNOVAR injection may cause muscle rigidity, particularly involving the muscles of respiration. This effect is due to the fentanyl component and is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs it is managed by the use of assisted or controlled respiration and by a neuromuscular blocking drug, if necessary.

FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD ALSO BE AVAILABLE.

Drug Dependence: *Fentanyl, the narcotic analgesic component, can produce drug dependence of the morphine type and therefore has the potential for being abused.*

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl, in this regard, has not been established, the use of INNOVAR injection or SUBLIMAZE fentanyl in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure: INNOVAR injection should be used with caution in patients who may be particularly susceptible to respiratory depression such as comatose patients who may have a head injury or brain tumor. In addition, these drugs may obscure the clinical course of patients with head injury.

Usage in Children: The safety of INNOVAR injection in children two years of age or younger has not been established.

Usage in Pregnancy: The safe use of INNOVAR injection has not been established with respect to possible adverse effects upon fetal development.

Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS *The initial dose of INNOVAR injection should be appropriately reduced in elderly, debilitated and other poor risk patients. The effect of the initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves, and can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms (see Actions) fentanyl and droperidol also depress respiration and blood pressure. Therefore, when INNOVAR injection is used to supplement these forms of anesthesia, the anesthetist must be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

The droperidol component of INNOVAR injection may decrease pulmonary arterial pressure. This fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient.

Vital signs should be monitored routinely.

INNOVAR injection, and SUBLIMAZE fentanyl, should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised ventilation. In such patients narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia this can be managed by assisted or controlled respiration. Postoperatively respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists (levallorphan, nalorphine, and naloxone); consult individual prescribing information before using.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INNOVAR injection. When patients have received such drugs, the dose of INNOVAR injection required will be less than usual. Likewise, following the administration of INNOVAR injection the dose of other CNS depressant drugs should be reduced.

INNOVAR injection should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in the moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus these other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INNOVAR injection due to the alpha-adrenergic blocking action of droperidol.

The fentanyl component may produce bradycardia, which may be treated with atropine; however, INNOVAR injection should be used with caution in patients with cardiac bradyarrhythmias.

When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

ADVERSE REACTIONS The most common serious adverse reactions reported to occur with INNOVAR injection are respiratory depression, apnea, muscular rigidity, and hypotension; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, twitching, blurred vision, hyperactivity on induction, laryngospasm, transient hypertension, nausea and emesis, diaphoresis, emergence delirium, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).

Postoperative drowsiness is also frequently reported.

OVERDOSAGE ***Manifestations:*** The manifestations of INNOVAR injection overdosage are an extension of its pharmacologic actions.

Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered. A specific narcotic antagonist such as nalorphine, levallorphan or naloxone should be available for use as indicated to manage respiratory depression caused by the narcotic component fentanyl. This does not preclude the use of more immediate countermeasures. Consult the package inserts for the individual narcotic antagonists for details about use.

HOW SUPPLIED INNOVAR® injection is supplied in 2 cc. (**NDC** 0045-0280-20) and 5 cc. (**NDC** 0045-0280-50) ampuls, in packages of 10.

IMPORTANT: Complete dosage information is available in insert which accompanies each package (or on request). The drug is available only upon direction of a physician.

U.S. Patent No. 3,141,823

9/74

McNEIL McNeil Laboratories, Inc.
Fort Washington, Pa. 19034

PROFESSIONAL INSTRUMENTS COMPANY MODEL NS-2 * PERIPHERAL NERVE STIMULATOR

MONITORS EFFECTS OF SKELETAL MUSCLE RELAXANTS ON THE NEUROMUSCULAR JUNCTION, DETECTING ABNORMAL RESPONSE TO MUSCLE RELAXANTS AND DISTINGUISHES BETWEEN DEPOLARIZING AND NON-DEPOLARIZING BLOCKADE.

THE MODEL NS-2

- ☐ **DELIVERS** STIMULI AT 5 SECOND INTERVALS. ONE OR FIFTY PULSES-PER-SECOND MAY BE SELECTED BY MOMENTARY PUSH-BUTTON SWITCHES.
- ☐ **OUTPUT** IS A MONOPHASIC SQUARE WAVE PULSE HAVING A RISE AND FALL TIME OF LESS THAN ONE MICROSECOND. AMPLITUDE OF PULSE IS LINEARLY ADJUSTABLE.
- ☐ **SOLID STATE**, RUGGED, BATTERY POWERED, PORTABLE AND LIGHTWEIGHT. THE USE OF INTEGRATED CIRCUITS ENSURES MAXIMUM RELIABILITY.
- ☐ **IT IS** THE RESULT OF AN AGGRESSIVE, CONTINUING RESEARCH AND DEVELOPMENT PROGRAM IN NERVE STIUMLATORS AND OTHER ELECTRONIC PRODUCTS BY PROFESSIONAL INSTRUMENTS COMPANY.

* MANUFACTURED UNDER U. S. DEVICE AND USE PATENT NO.'S 3,364,929 • 3,565,080 • 3,612,060 3,624,484 • 3,682,162

FOR INFORMATION, CONTACT: Professional Instruments Company
SUITE C5
4800 WEST 34TH ST.
HOUSTON, TEXAS 77018
PHONE (713) 681-1362

U.S. Patent applied for.

Ref: Corneal Injuries During General Anesthesia, Anesthesia and Analgesia, Vol. 54, No. 4, July-August, 1975

Protect patients' eyes with OPTI-GARD™

Why tape eyelids shut and risk skin abrasion, loss of eyelashes, and contact dermatitis? Dupaco Opti-Gard,™ for use during general anesthesia and post-op recovery, effectively and comfortably helps prevent corneal abrasion, lacerations, and scleral hemorrhage. Opti-Gard™ also protects against blood, fluid, or other foreign materials entering the eyes . . . a vital consideration in ENT, head, or neck surgery. Sterile packaged and boxed in convenient dispenser, Opti-Gard™ clear plastic protective covers come with self adhesive foam cushion. **Send for free sample.**

DUPACO INCORPORATED

P.O. Box 98, San Marcos, Ca. 92069

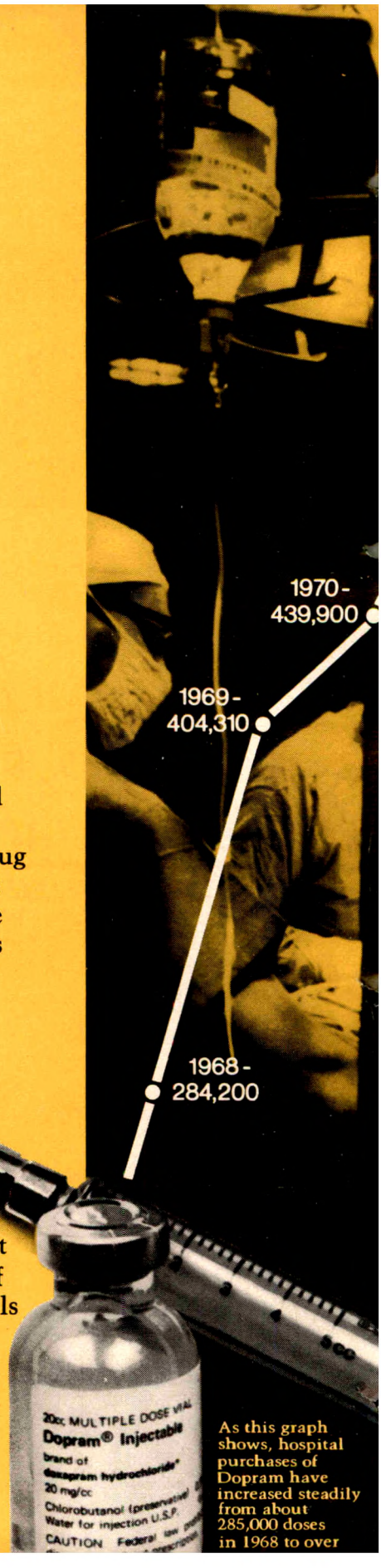
In all types of hospitals across the United States, its usage grows–

Dopram®
Injectable
(doxapram HCl)

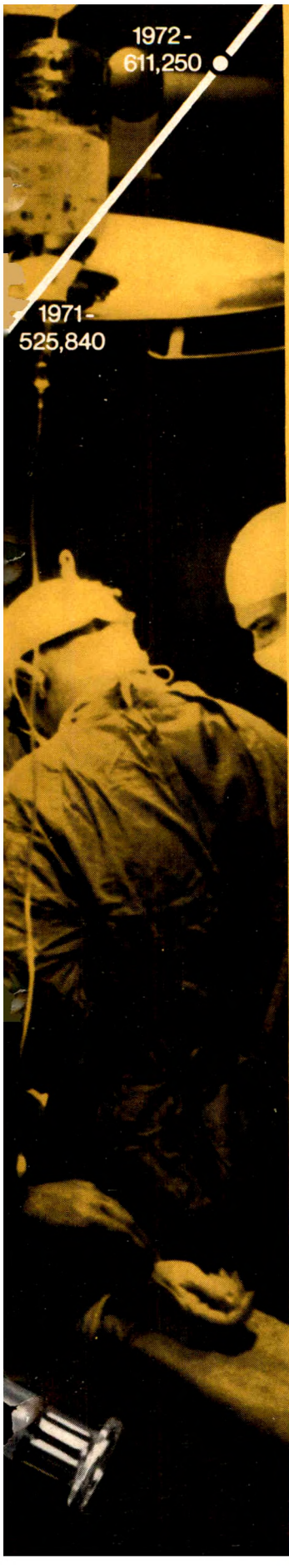
Seven years ago, A. H. Robins introduced Dopram, a unique respiratory stimulant developed in the company's research laboratories. What made this drug so useful to the anesthesiologist was its ability to rapidly restore the respiratory drive in patients with drug-induced post anesthetic depression.

Usage of Dopram has been steadily increasing each year, until today it has become a very important drug in the armamentarium of more than 1,500 hospitals of all types in all 50 states, the District of Columbia, and a number of foreign countries. These hospitals purchased more than 600,000 doses in 1972 alone.

Dopram–an important drug in anesthesiology. Try it for sighs!



As this graph shows, hospital purchases of Dopram have increased steadily from about 285,000 doses in 1968 to over



Indications

1. To stimulate respiration in patients with drug induced post-anesthetic respiratory depression or apnea other than that due to muscle relaxant drugs.
2. To pharmacologically stimulate deep breathing in the so-called "stir-up" regimen in the post-operative patient. Simultaneous administration of oxygen is desirable.
3. To hasten arousal and return of protective pharyngeal and laryngeal reflexes.
4. To aid in the differential diagnosis of post-anesthetic respiratory depression. Failure to adequately stimulate respiration suggests residual muscle relaxant effect.
5. To stimulate respiration, hasten arousal and to encourage the return of laryngopharyngeal reflexes in patients with mild to moderate respiratory and CNS depression due to drug overdosage.

Contraindications—Epilepsy and other convulsive states: incompetence of the ventilatory mechanism due to muscle paresis, flail chest, pneumothorax, airway obstruction, and extreme dyspnea; severe hypertension and cerebrovascular accidents; hypersensitivity.

Doxapram is not recommended for patients 12 years of age or under because studies to evaluate its safety and efficacy have not been performed.

Warnings—Doxapram is an analeptic agent; it is neither an antagonist to muscle relaxant drugs nor a specific narcotic antagonist. Since doxapram has an acid pH, it should not be mixed with alkaline solutions such as thiopental sodium.

Since narcosis may recur after stimulation with doxapram, care should be taken to maintain close observation until the patient has been fully alert for 1/2 to 1 hour. (Duration of drug 5-12 minutes.)

Doxapram is an adjunct to well-accepted supportive measures and resuscitative techniques. It may not stimulate adequate spontaneous breathing or provide sufficient arousal in patients who are severely depressed with CNS depressant drugs.

When doxapram is administered to postoperative patients or to patients in a state of narcosis with chronic pulmonary insufficiency, oxygen should be administered concomitantly. Failure to do so may result in further oxygen debt and more severe dyspnea due to the increased work of breathing.

Doxapram should be administered with great care and only under close supervision to patients with cerebral edema, bronchial asthma, severe tachycardia, cardiac arrhythmia, cardiac disease, hyperthyroidism and pheochromocytoma.

Usage in pregnancy

No adequate clinical studies have been performed to determine the safe use of doxapram in pregnancy. Until further clinical experience has been obtained, the physician must weigh the need against possible risks in using the drug in pregnant patients or in women of child-bearing potential.

Precautions—Recommended dosages of doxapram should be employed and maximum total dosages should not be exceeded. In patients with advanced pulmonary disease with hypoxemia, marked respiratory stimulation increases the work of breathing and may, thus, increase oxygen consumption and carbon dioxide production.

With excessive dosage, hyperventilation induced by doxapram may lead to respiratory alkalosis and hypocapnia with tetany and, theoretically, apnea.

An adequate airway is essential. In order to avoid side effects, it is advisable to use the minimum effective dosage. Monitoring of the blood pressure and deep tendon reflexes is recommended to prevent overdosage.

It is desirable that blood gases (P_{O_2} P_{CO_2} O_2 saturation) be monitored to assess the effectiveness of respiratory stimulation.

Intravenous barbiturates, oxygen and resuscitative equipment should be readily available to manage overdosage manifested by excessive central nervous system stimulation. Slow administration of the drug and careful observation of the patient during administration and for some time subsequently are advisable to insure restoration of the protective reflexes. The possibility of post-stimulation respiratory depression must be kept in mind. In patients who have been lightly curarized, doxapram may temporarily mask the residual effects of muscle relaxant drugs.

Doxapram should be administered cautiously to patients receiving sympathomimetic or monoamine oxidase inhibiting drugs, since a synergistic pressor effect may occur. It should likewise be used with care in post-operative patients with marked dyspnea due to obstructive pulmonary emphysema, acute or chronic asthma, profound metabolic disorders, severe to moderately severe hypertension, increased cerebrospinal fluid pressure, head injury and acute agitation.

Since doxapram may stimulate basal gastric secretion, it should be used with care in patients with peptic ulcer disease and in patients undergoing gastric surgery.

Vascular extravasation or use of a single injection site over an extended period should be avoided since either may lead to thrombophlebitis.

Hypocapnia accompanying forced ventilation is a potent stimulus to cerebral vasoconstriction; it may be postulated that some element of risk may exist from reduced cerebral blood flow following prolonged and intensive hyperventilation.

Since an increase in epinephrine release has been noted with doxapram, it is recommended that initiation of therapy with this respiratory stimulant be delayed for at least 10 minutes following the discontinuance of anesthetics known to sensitize the myocardium to catecholamines, such as halothane and cyclopropane.

As with other intravenous preparations, all precautions should be taken during administration of doxapram to insure that injection is made directly into a suitable vein; extravasation, and inadvertent intra-arterial injection should be avoided.

Adverse reactions—The following adverse reactions have been reported: *Central and Autonomic Nervous Systems.* Hyperactivity feeling of warmth, sweating, muscle tremor, clonus, increased deep tendon reflexes, dizziness, muscle spasticity, pyrexia, confusion, paresthesia, pupillary dilatation, pilomotor erection, headache, bilateral babinski, fasciculation and carpopedal spasm. A grand mal seizure occurred 95 minutes after drug administration in a known epileptic patient who was on anticonvulsant medication.

Respiratory. Cough, dyspnea, laryngospasm bronchospasm and hiccough.

Cardiovascular. Hypertension, sinus tachycardia, bradycardia, extrasystoles, lower T-waves, premature ventricular contractions, irregular heart rhythm, tightness in chest. Although a mild to moderate increase in blood pressure is not infrequent, such an increase may occasionally be of concern in hypertensive patients.

Gastrointestinal. Nausea and/or vomiting, salivation, stimulation of lower bowel, sour taste.

Genitourinary. Urinary retention, stimulation of urinary bladder with spontaneous voiding.

Miscellaneous. Pruritus, thrombophlebitis.

Laboratory Determinations. A decrease in hemoglobin, hematocrit, or red blood cell count has been observed in postoperative patients. In the presence of pre-existing leukopenia, a further decrease in WBC was observed following anesthesia and treatment with doxapram hydrochloride. Elevation of BUN and albuminuria have been observed.

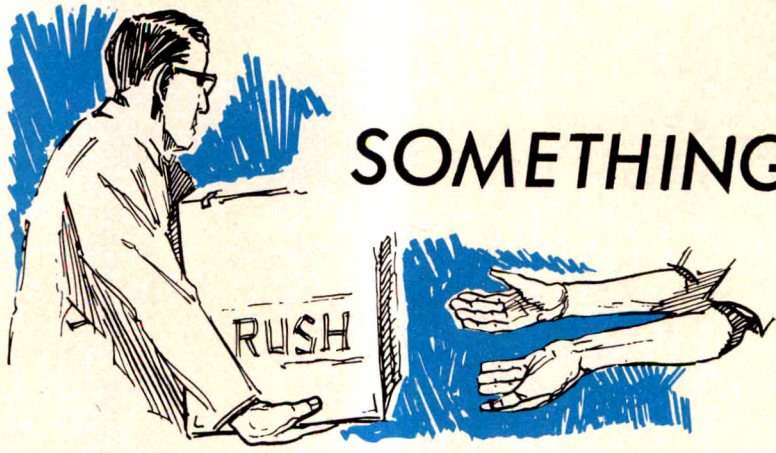
In some of the cases cited above, the patients had received multiple drugs concomitantly, thus preventing an absolute judgment as to the role of doxapram in these reactions.

Dosage—For complete information concerning dosage and administration see package insert.

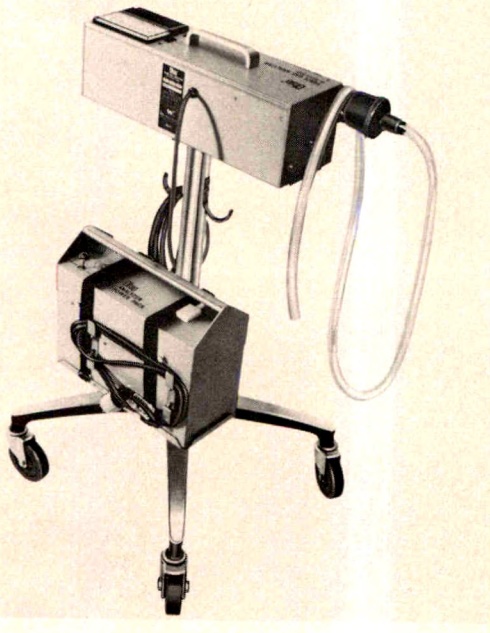
Supply—Dopram (doxapram hydrochloride) is available in 20 cc rubber-stoppered vials containing 20 mg/cc, with chlorobutanol 0.5% as the preservative.

A. H. Robins Company
Richmond, Virginia 23220

A·H·ROBINS



SOMETHING NEW



Ohio Medical Products, Madison, Wisconsin, has available an instrument for ambient air contamination analysis known as the OHIO Trace Gas Analyzer. It is designed to provide rapid and continuous measurement of nitrous oxide pollution in operating rooms and elsewhere. It can be employed to test exhaust systems for escaping nitrous oxide, and to detect equipment leakage both through time period analysis of ambient conditions as well as source identification.

★ ★ ★

Informatics Inc., Woodland Hills, California, a world leader in computer services, has just released two new brochures describing its extensive, computerized medical information data base, Excerpta Medica On-Line (EMOL) Service.

This EMOL Service resulted from a cooperative agreement between the Excerpta Medica Foundation, long a major source for the dissemination of medical information to the world's health care professionals, and Informatics Inc.

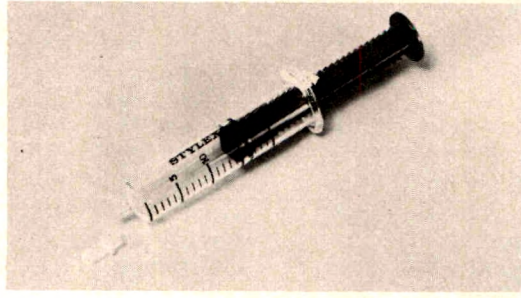
EMOL provides extensive coverage of the world's biomedical literature and offers instant retrieval capability on a retrospective or continuing basis, thus permitting researchers, clinicians, program administrators, pharmaceutical manufacturers access to the bibliographic material through a simple typewriter-like computer terminal that can be used in any office or laboratory.

Columbus Instruments International Corporation, Columbus, Ohio, presents their "CARDIOTHERM-500." It automatically measures and tracks blood temperature via the same thermistor catheter which is used for thermodilution curve sensing. It also automatically measures and tracks the indicator temperature. The only parameter left for manual entry is the volume of indicator. Any volume can be entered on the digital dial—0 to 10 mL in increments 0.01 mL.

The "CARDIOTHERM-500" is rechargeable battery-operated and, using a special power-saving circuit, the battery will last for 100 cardiac output measurements independent of the time of use.

★ ★ ★

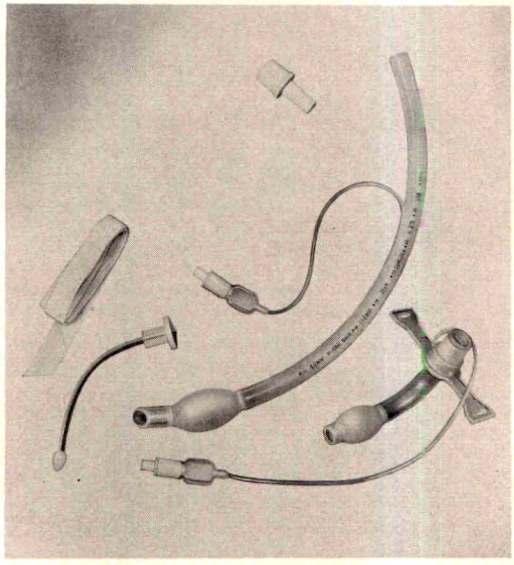
Pharmaseal, Glendale, California, has a new 10 cc medication device which features a special ratchet plunger design that eliminates the numerous problems that may arise, eg, when disconnetcing syringes from IV lines, or the need for check valves, slide clamps and tubes. Also, Stylox's ratchet design means you can inject incremental doses precisely.



★ ★ ★

Shiley Laboratories, Inc., Irvine, California, announces their new disposable radiopaque tracheostomy tube, with a new thin-walled, high volume low pressure cuff and a new pressure relief valve to prevent tracheal damage due to cuff overinflation. The relief valve prevents internal cuff pressures in excess of 25 mmHg by venting off excess air.

Additional features of the new tracheostomy tube include an inner cannula with locking 15 mm connector, easily removed and cleaned to maintain a patent airway without changing the entire tube, and a swivel neck plate for maximum comfort and conformity to individual neck anatomies. The obturator is tapered to simplify insertion and minimize trauma.



Medical Engineering Corporation, Racine, Wisconsin, has available the "Surgitek® Silicone Anesthesia Tubes" with the exclusive Surgitek® low trauma cuff. The all-silicone tube is soft, pliable, and is claimed to be more comfortable for the patient, and much less likely to cause necrosis. The Surgitek® tubes may be steam or gas sterilized.

★ ★ ★

Wolff Industries, San Marino, California, have a new product, the MR-81 Physiological Data Tape Recorder. Eight channels of physiological data may be recorded on a compact cassette.

This instrument finds use in recording a wide variety of physiological parameters such as ECG, EEG, blood pressure, blood flow, pulse wave forms and heart sounds. The MR-81 Recorder utilizes both FM and PPM modulation technics. Additionally, one channel may be temporarily interrupted with voice comments by using the press-to-talk microphone that is furnished.

★ ★ ★

A three channel electrocardiograph capable of producing a complete 12-lead electrocardiogram in 10 seconds is now available from the Burdick Corporation, Milton, Wisconsin. The Burdick model EK-6 simultaneously records three leads, offering physicians and technicians maximum accuracy and diagnostic data while maintaining the simplicity and ease of operation of single channel ECGs.

It is suitable for use in hospitals, multiphasic screening centers, physician offices, or any other facility where there is daily need for specific, accurate, electrocardiographic service.

★ ★ ★

Advanced Instrumentation Corporation, Middleton, Wisconsin, has a new blood pressure monitor which is noninvasive, nonocclusive, atraumatic and offers continuous pressure readout in addition to continuous pulse pressure recording or CRT display. A small force transducer held in place on the wrist with a Velcro strip provides input data to this new Model ML-10.

THE VULNERABLE EYE.

Lacri-Lube® protects the vulnerable eye of the anesthetized patient.

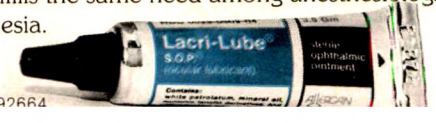
The under-protected eye is threatened during general anesthesia. Tape alone can leave your patient's eye vulnerable to dehydration and corneal erosion. And with medicated ointments, you unnecessarily risk allergic reactions and possible long-term sensitization.

Lacri-Lube meets your need for a safer, more sophisticated method of protecting and lubricating the eye. Either on its own or as an adjunct to taping. It's the first non-medicated, sterile ophthalmic ointment specifically designed to lubricate and protect the eye—and do nothing more.

In fact, ophthalmologists have established Lacri-Lube as their lubricant-protectant of choice whenever an eye is jeopardized by exposure or dehydration. And the rapid increase in its surgical use indicates that Lacri-Lube fulfills the same need among anesthesiologists.

Lacri-Lube is the ophthalmic for anesthesia.

When you consider the alternatives, you can't make a better choice.



ALLERGAN
Irvine, CA 92664

ANTILIRIUM
(Physostigmine Salicylate)

REVERSES MOST POST-OPERATIVE DELIRIUM AND PROLONGED SOMNOLENCE

Before prescribing, please consult complete product information, a summary of which follows:

ACTION: ANTILIRIUM (physostigmine salicylate) is a salicylic acid derivative of an alkaloid extracted from seeds of Physostigma Venenosum (calabar bean). The action of the parasympathetic nerves is intermediated by the formation of acetylcholine at the peripheral end of these nerves. Physostigmine inhibits the destructive action of cholinesterase and thereby prolongs and exaggerates the effect of the acetylcholine.

Physostigmine contains a tertiary amine and easily crosses the blood brain barrier, while neostigmine contains a quaternary amine and is not capable of crossing the structure. This may explain why neostigmine does not cause reversal of anticholinergic-induced delirium while physostigmine does.

INDICATIONS: TO REVERSE THE TOXIC EFFECTS UPON THE CENTRAL NERVOUS SYSTEM CAUSED BY DRUGS IN CLINICAL OR TOXIC DOSAGES CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING.

SEVERE ANTICHOLINERGIC POISONING MAY PRODUCE: COMA, MEDULLARY PARALYSIS AND DEATH.

CENTRAL TOXIC EFFECTS MAY INCLUDE: HALLUCINATIONS, DELIRIUM, DISORIENTATION, ANXIETY AND HYPERACTIVITY.

Dramatic reversal within minutes of coma, hallucinations, and other signs can be expected if the diagnosis is correct and the patient has not suffered anoxia or other insult. Therapeutic doses may be necessary at intervals as life-threatening signs recur. Physostigmine is destroyed in the body in 60 to 120 minutes.

CONTRAINDICATIONS: Physostigmine should not be used in the presence of asthma, gangrene, diabetes, cardiovascular disease, mechanical obstruction of the intestines or urogenital tract or any vagotonic state, and in patients receiving choline esters or depolarizing neuromuscular blocking agents.

WARNING: If excessive symptoms of salivation, emesis, urination and defecation occur, the use of ANTILIRIUM should be terminated. If excessive sweating or nausea occur, the dosage should be reduced.

Intravenous administration should be at a slow, controlled rate, no more than 1 mg. per minute (see dosage). Rapid administration can cause bradycardia, hypersalivation leading to respiratory difficulties and possibly convulsions.

An overdosage of ANTILIRIUM can cause a cholinergic crisis.

PRECAUTIONS: Because of the possibility of hypersensitivity in an occasional patient, atropine sulfate injection should always be at hand since it is an antagonist and antidote for physostigmine.

ADMINISTRATION AND DOSAGE: The usual adult dose of ANTILIRIUM is 0.5 to 2.0 mg. intramuscularly or intravenously. Intravenous administration should be at a slow, controlled rate of no more than 1 mg. per minute. It may be necessary to repeat dosages of 1 mg. to 4 mg. at intervals as life threatening signs such as arrhythmias, convulsions and deep coma recur.

IN ALL CASES OF POISONING, THE USUAL SUPPORTIVE MEASURES SHOULD BE UNDERTAKEN.

SUPPLIED: 2 ml. ampules containing: PHYSOSTIGMINE SALICYLATE 1 mg. per ml. Packed 12 ampules per box.

NDC 0456-1037-12

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES:

Greene, L. T.: Physostigmine treatment of anticholinergic drug depression in postoperative patients. Anesth & Analg, March-April 1971; 50-2: 222-226.

Rumack, B.: Anticholinergic poisoning: Treatment with physostigmine. Pediatrics, Sept. 1973.

Slovis, T. L., Ott, J. E., Tietelbaum, D. T., and Lipscomb, W.: Physostigmine therapy in acute tricyclic antidepressant poisoning. Clinical Toxicology, 4:451, 1971.

DRUGS AND CHEMICALS CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING:

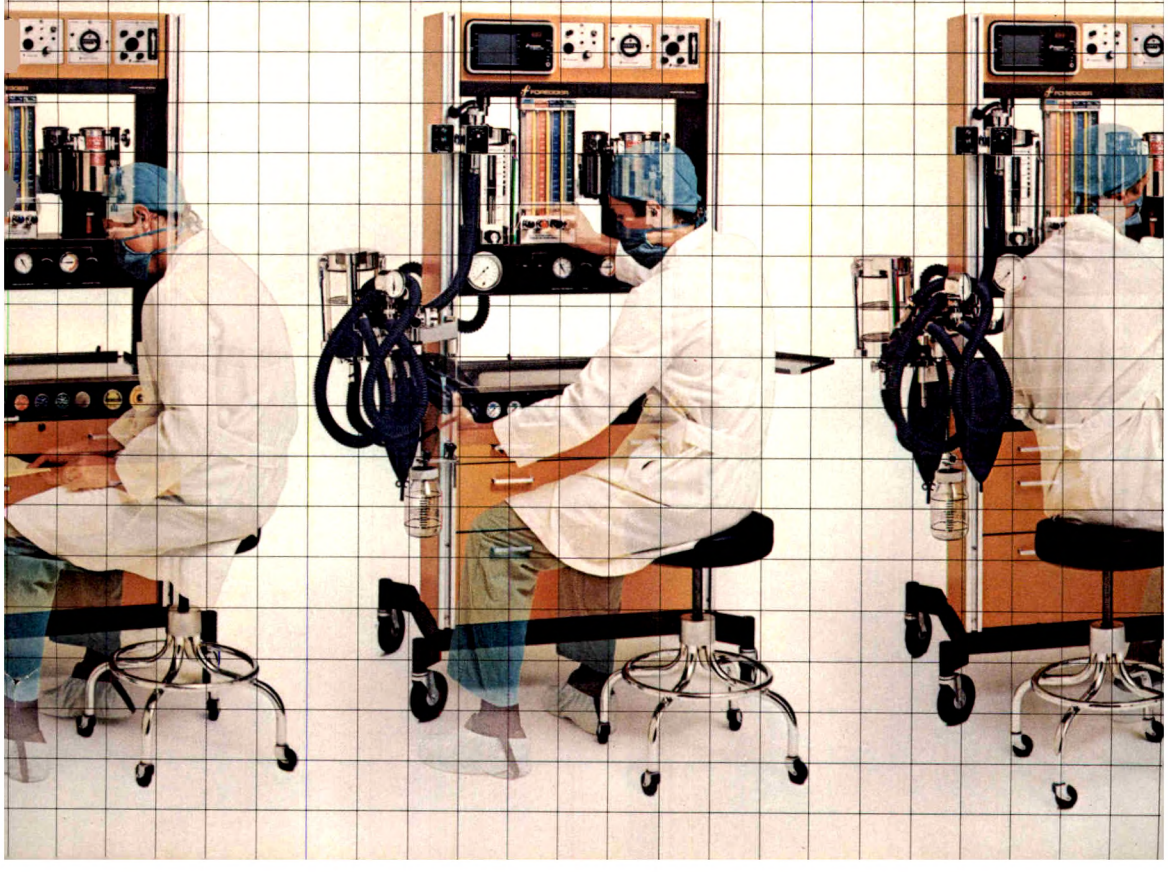
- AMITRIPTYLINE (Elavil, Triavil, Etrafon)
- ANISOTROPINE METHYLBROMIDE
- ATROPINE
- BELLADONNA
- BENACTYZINE
- CHLORPHENIRAMINE
- CYCLOPENTOLATE
- DESIPRAMINE (Norpramin, Pertofrane)
- DICYCLOMINE
- DIPHENHYDRAMINE
- DOXEPIN (Sinequan)
- HOMATROPINE
- HYOSCINE
- HYOSCYAMUS
- IMIPRAMINE (Tofranil, Presamine)
- ISOPROPAMIDE
- MEPENZOLATE
- METHANTHELINE
- METHAPYRILENE
- NORTRIPTYLINE (Aventyl)
- PIPENZOLATE BROMIDE (Piptal)
- PROPANTHELINE
- PROTRIPTYLINE (Vivactil)
- PYRILAMINE
- SCOPOLAMINE
- STRAMONIUM
- PHENOTHIAZINES
- TRICYCLIC ANTIDEPRESSANTS (Aventyl, Elavil, Etrafon, Norpramin, Pertofrane, Presamine, Tofranil, Triavil, Vivactil)
- THIORIDAZINE (Mellaril)

O'NEAL, JONES & FELDMAN, INC.

1304 ASHBY ROAD • ST. LOUIS, MISSOURI 63132 • (314) 997-6650

Introducing The Human-Engineered Anesthesia Control Center.

The FOREGGER® 710



The FOREGGER 710

Anesthesia Control Center.

Unlike Anything You've Ever Seen.

Think of what it is like using a typical anesthesia machine. Now, look at the new FOREGGER 710 Anesthesia Control Center. Notice the completeness, compactness, accessibility and visibility of the components. Everything is in one place, within reach . . . without dangling wires and add-on components. That's why we call it the FOREGGER 710 Anesthesia Control Center.

Unlike existing anesthesia machines, the FOREGGER 710 Anesthesia Control Center is human engineered. The design revolves around you. All of the controls for both fixed and movable components are operated from a comfortable, working position. And this ease of control is complemented by the latest innovations in anesthesia equipment design.

Take, for instance, the unique rotating Vaporizer Turret. It accommodates up to three vaporizers, including the Foregger Copper Kettle® Vaporizer and Foregger Direct Reading Vaporizers. When the Turret is locked into place, there is no doubt which vaporizer is in circuit. Possible contamination from anesthetic agents contained in the other vaporizers is eliminated.

Then there are the Direct Reading Vaporizers designed for the administration of a specific liquid anesthetic, over a wide range of temperatures and flow rates. The Copper Kettle Vaporizer, on the other hand, affords you constant and precise control in both increments and decrements, while providing simple and accurate administration of an anesthetic agent.

There's also a built-in Anesthesia Ventilator that features fluidic circuitry, independent controls, and a mode selector switch that enables you to transfer from ventilator to bag without changing tubes or adjusting the pressure relief valve. It gives you the convenience of easy readouts and the efficiency of direct control. And it's easy to clean.

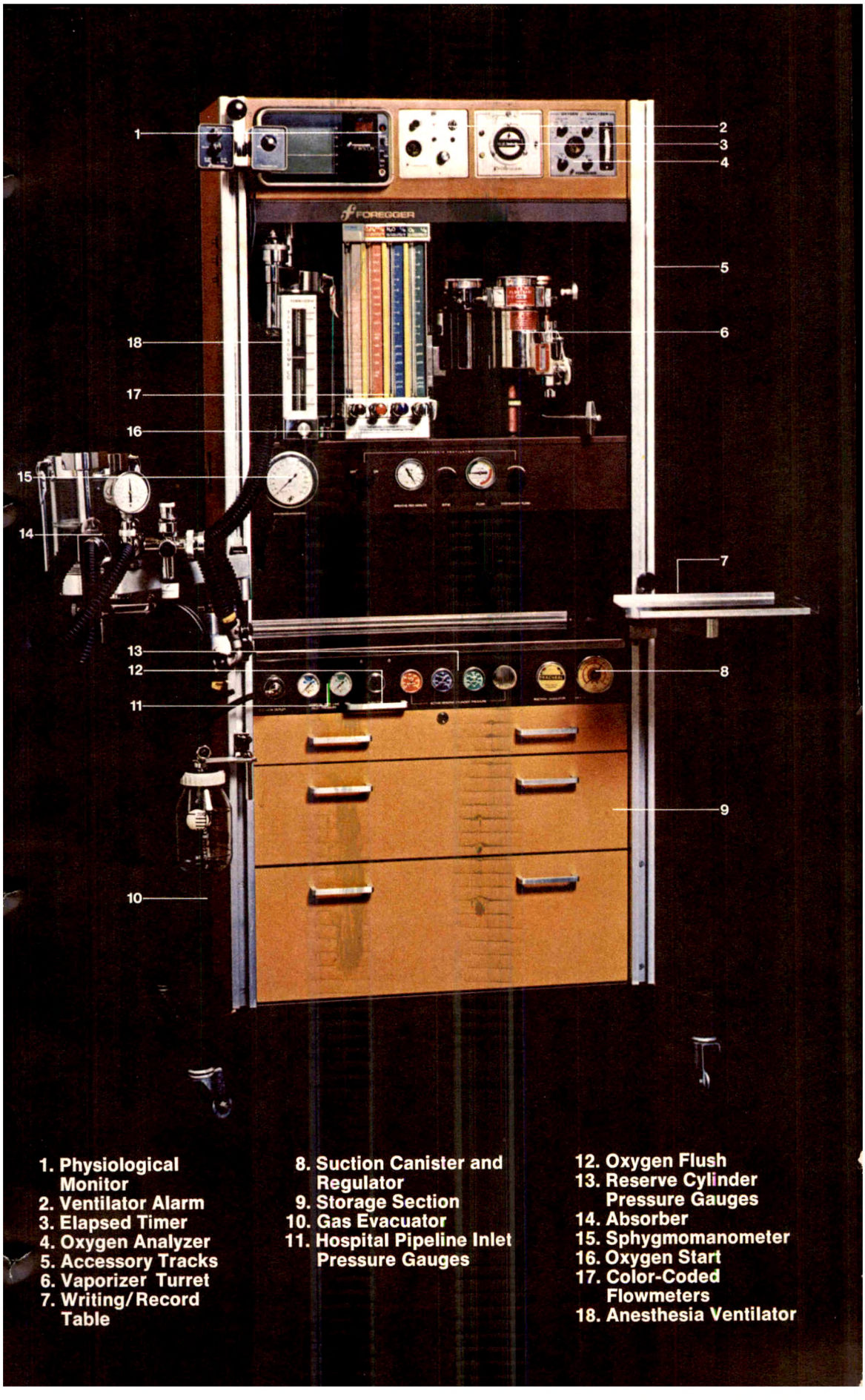
Storage is human-engineered too! Cabinetry in the new FOREGGER 710 Anesthesia Control Center combines linear designed storage with easy accessibility and large capacity.

The Monitoring System, which provides a wide range of physiological monitoring capability, is located where you need it during procedures. Easy to see and reach, it includes a physiological monitor (ECG, EEG, temperature, pulse rate, and pressure), an Oxygen Analyzer, Ventilator Disconnect Alarm, and an Elapsed Timer.

In addition, the FOREGGER 710 Anesthesia Control Center has a built-in Oxygen Start, which automatically shuts off all other gases when the oxygen flow is reduced to a predetermined level. Plus, four parallel accessory tracks to mount and adjust FOREGGER 710 Anesthesia Control Center accessories. All of which add another dimension to overall flexibility.

And that's where you should place the new FOREGGER 710 Anesthesia Control Center. Over all. In capabilities. Flexibilities. And human engineering. Take a look at its other unlike features and we think you'll agree . . . The FOREGGER 710 Anesthesia Control Center is unlike anything you have seen before. For more information about what human engineering with everything in one place can mean to you, fill out and return the attached card.

With FOREGGER—It's The Unlikely Things About Us That You'll Like.



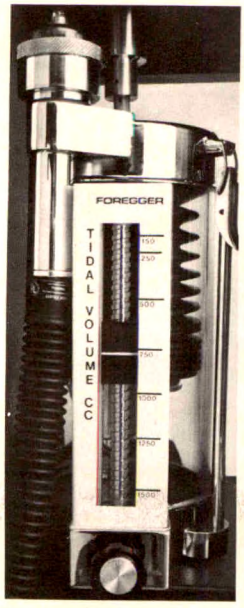
1. Physiological Monitor
2. Ventilator Alarm
3. Elapsed Timer
4. Oxygen Analyzer
5. Accessory Tracks
6. Vaporizer Turret
7. Writing/Record Table
8. Suction Canister and Regulator
9. Storage Section
10. Gas Evacuator
11. Hospital Pipeline Inlet Pressure Gauges
12. Oxygen Flush
13. Reserve Cylinder Pressure Gauges
14. Absorber
15. Sphygmomanometer
16. Oxygen Start
17. Color-Coded Flowmeters
18. Anesthesia Ventilator

The FOREGGER 710

Anesthesia Control Center.

Everything Built-In, Not Added-On.

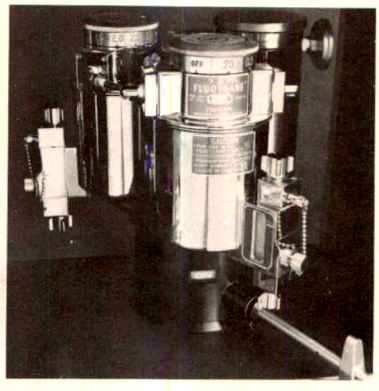
1



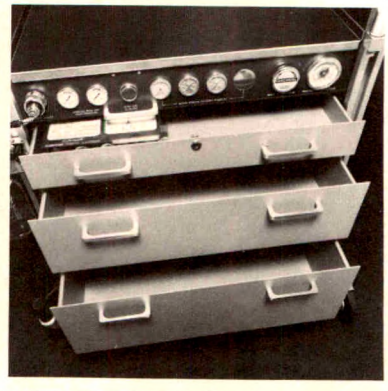
1) Built-In Ventilator
2) Vaporizer Turret
3) Deep-Dish Storage
4) Oxygen Start
5) Accessory Tracks

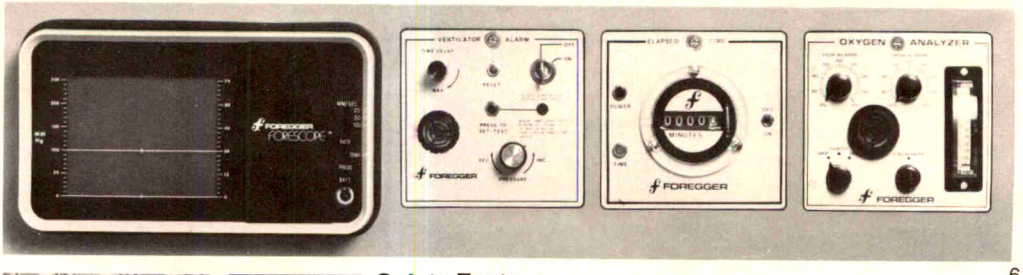
6) Patient Monitoring Console
   a) ECG, EEG, Temperature, Pulse Rate, Pressures
   b) Ventilator Disconnect Alarm
   c) Elapsed Timer
   d) Oxygen Analyzer

2

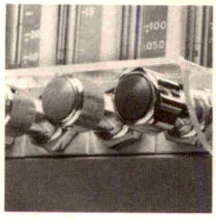


3

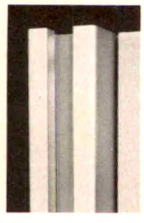




6



4



5

Safety Features

Incorporates many of the latest safety standards as recommended by the Z-79/CGA

Service from one source

Vaporizer Turret
Oxygen Analyzer
Ventilator Disconnect Alarm
Patient Monitoring
Low Pressure Guardian® System

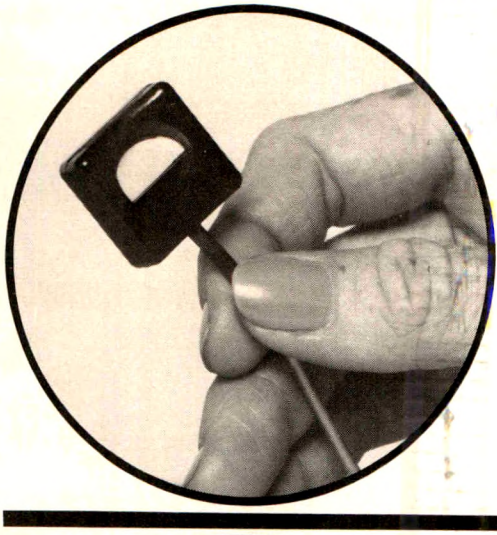
Human engineered for optimal accessibility and visibility of components

Efficient Gas Evacuator

Oxygen Start System

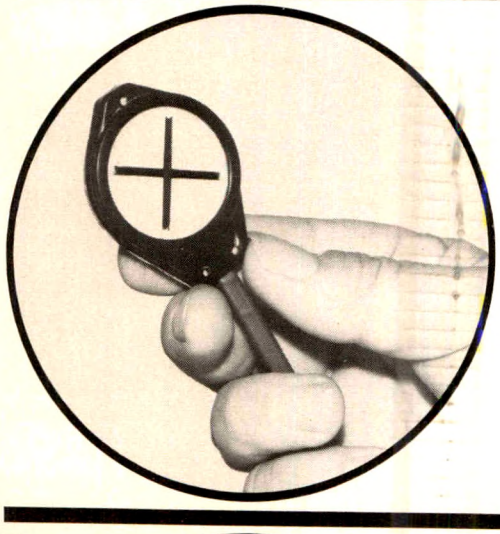
Air Products
FOREGGER®

VERSATONE® MULTI-PURPOSE DOPPLER INSTRUMENT



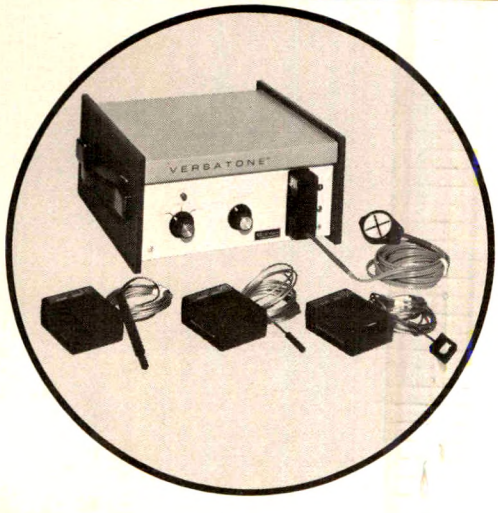
FOR MONITORING DOPPLER SOUNDS OF BLOOD FLOW AND TO TAKE DOPPLER SYSTOLIC BLOOD PRESSURE

This sensitive Doppler probe is easy to tape in position for non-invasive detection and monitoring of arterial blood flow during surgery. Used with an occlusive cuff and manometer, systolic blood pressures may be obtained even on infants and hypotensive patients.



FOR EARLY DETECTION OF VENOUS AIR EMBOLISM

This sensitive wide-angle Doppler probe is particularly well suited for the detection of venous air emboli which may occur during neurosurgical procedures performed with the patient in the upright position. It also detects motion of the heart muscle, heart valves and blood flow.



VERSATONE D8 DOPPLER

The Model D8 VERSATONE Doppler instrument is designed to use interchangeable probes of various frequencies and configurations. It is powered by a rechargeable battery and has a built-in loudspeaker. Options include an electrocautery sensor and cut-out, a molded earset for private listening, and a chart recording circuit. The two probes shown above are particularly useful to the anesthesiologist. Two sizes of pencil shaped probes are also available. These are useful for intraoperative assessment of flow in exposed vessels, as well as for transcutaneous flow detection.

MED SONICS

For more information call or write:
P.O. Box M (340 Pioneer Way) Mountain View, CA (415) 965-3333

ANECTINE
(succinylcholine chloride)
For controlled muscle relaxation adjunctive to anesthesia:

FLO-PACK® for prolonged relaxation

- instant-mix sterile powder interfaces with all major parenteral systems (vacuum or nonvacuum)
- each unit complete—no needle or syringe needed
- retains potency indefinitely
- no refrigeration required
- unbreakable, sterile plastic injection units of 500 and 1,000 mg

INJECTION for short-term relaxation

- a product of choice for intubation and other short procedures
- unique square bottle and bright yellow label for positive identification
- ready for immediate use
- 20 mg per cc . . . in 10 cc multidose vials
- flip-top cap for easy opening
- single or multiple use

ANECTINE®
(succinylcholine chloride)
THE LONG AND SHORT of surgical muscle relaxation

THIS DRUG SHOULD BE USED ONLY BY INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS AND HAZARDS.

DESCRIPTION: Anectine brand Succinylcholine Chloride is an ultra short-acting depolarizing type muscle relaxant. Chemically it is a di-quaternary base consisting of the di-chloride salt of the di-choline ester of succinic acid. It is a white, odorless, slightly bitter powder and very soluble in water. The drug is unstable with alkaline solutions, but relatively stable in acid solutions depending upon the concentration of the solution and the storage temperature. While solutions of succinylcholine chloride are sterilized by autoclaving, they should, nevertheless, be stored under refrigeration to preserve their potency.

INDICATIONS: Succinylcholine chloride is indicated as an adjunct to anesthesia to induce skeletal muscle relaxation. It may be employed to reduce the intensity of muscle contractions of pharmacologically or electrically induced convulsions.

CONTRAINDICATIONS: Succinylcholine is contraindicated for persons with a known hypersensitivity to the drug.

WARNINGS:

WARNING: SUCCINYLCHOLINE SHOULD BE USED ONLY BY THOSE SKILLED IN THE MANAGEMENT OF ARTIFICIAL RESPIRATION AND ONLY WHEN FACILITIES ARE INSTANTLY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND FOR PROVIDING ADEQUATE VENTILATION OF THE PATIENT, INCLUDING THE ADMINISTRATION OF OXYGEN UNDER POSITIVE PRESSURE AND THE ELIMINATION OF CARBON DIOXIDE.. THE CLINICIAN MUST BE PREPARED TO ASSIST OR TO CONTROL RESPIRATION.

Succinylcholine should not be mixed with short-acting barbiturates in the same syringe, or administered simultaneously during intravenous infusion through the same needle. Solutions of succinylcholine have an acid pH whereas those of barbiturates are alkaline in reaction. Depending upon the resultant pH of a mixture of solutions of these drugs, either free barbituric acid may be precipitated or succinylcholine hydrolyzed.

Usage in Pregnancy. The safe use of succinylcholine has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

PRECAUTIONS: Low levels of, or abnormal variants of plasma cholinesterase may be associated with prolonged respiratory depression or apnea following the use of succinylcholine. Low levels of plasma cholinesterase may occur in patients with severe liver disease or cirrhosis, severe anemia, malnutrition, severe dehydration, changes in body temperature, exposure to neurotoxic insecticides or those receiving antimalarial drugs. Succinylcholine should be administered with extreme care to such patients and dosage should be minimal. If low plasma cholinesterase activity is suspected, a small test dose of from 5 to 10 mg of succinylcholine may be administered, or relaxation may be produced by the cautious administration of a 0.1% solution of the drug by intravenous drip. Drugs which either inhibit plasma cholinesterase, such as neostigmine or phospholine iodide, or compete with succinylcholine for the enzyme, as does intravenous procaine, should not be given concurrently with succinylcholine.

Succinylcholine should be administered with great caution to patients with severe burns, those recovering from severe trauma, those suffering from electrolyte imbalance, those receiving quinidine, those who have been digitalized recently or who may have digitalis toxicity as serious cardiac arrhythmias or cardiac arrest may result. Great caution should be observed also in patients with pre-existing hyperkalemia or who are paraplegic, have suffered spinal neuraxis injury, or have degenerative or dystrophic neuromuscular disease, as such patients tend to become severely hyperkalemic when succinylcholine is given.

When succinylcholine is given over a prolonged period of time, the characteristic depolarization block of the myoneural junction may change to a non-depolarizing block which results in prolonged respiratory depression or apnea. Under such circumstances, small repeated doses of neostigmine may possibly act as an antagonist. A peripheral nerve stimulator (e.g., the Wellcome Peripheral Nerve Stimulator) may be used to ascertain the type of neuromuscular blockade. If a depolarization block is present both fast (tetanic) and slow (twitch) rates of nerve stimulation are well sustained, and post-tetanic facilitation is absent. If a non-depolarizing block is present there is post-tetanic facilitation and "fade" of successive stimuli on both fast (tetanic) and slow (twitch) rates of nerve stimulation.

Succinylcholine should be used with caution during ocular surgery and in patients with glaucoma. The drug should be employed with caution in patients with fractures or muscle spasm as the muscle fasciculations may cause additional trauma. Muscle fasciculations and hyperkalemia may be reduced by administering a small dose of a non-depolarizing relaxant. If other relaxants are to be used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered.

During the past few years, reports have called attention to a fulminant syndrome, malignant hyperthermia, observed during anesthesia. Its etiology is not fully understood. Malignant hyperthermia occurs in genetically prone individuals of all ages and both sexes receiving potent anesthetics such as halothane, methoxyfluothane, cyclopropane and diethyl ether. It appears to develop irrespective of the concomitant use of a muscle relaxant, but may be triggered by succinylcholine. Because of the seriousness of this syndrome and the need for early effective treatment of the patient, it is suggested that the continuous monitoring of the temperature will serve as an aid to the early recognition of malignant hyperthermia.

ADVERSE REACTIONS: Adverse reactions consist primarily of an extension of the drug's pharmacological actions. Profound and prolonged muscle relaxation may occur, resulting in respiratory depression to the point of apnea. Hypersensitivity to the drug may exist in rare instances.

The following adverse reactions have been reported: bradycardia, tachycardia, hypertension, hypotension, arrhythmias, cardiac arrest, prolonged respiratory depression or apnea, hyperthermia, increased intraocular pressure, muscle fasciculation, postoperative muscle pain, myoglobinemia and excessive salivation.

MANAGEMENT OF ADVERSE REACTIONS: Apnea or prolonged muscle paralysis should be treated with controlled respiration.

The use of neostigmine to reverse a non-depolarization block is a medical decision which must be made upon the basis of the individual clinical pharmacology and the experience and judgment of the clinician. When neostigmine is used atropine should also be administered.

SUPPLIED: Injection, Multi-dose vials, 20 mg cc, 10 cc, boxes of 12 vials. Flo-Pack® Sterile Powder 500 mg and 1,000 mg, boxes of 12.

Complete literature available on request from Professional Services Dept. PML.

Wellcome
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

212-978-6900 516-546-5511

800-645-2059

MEDICAL MANAGEMENT CO.

A National Organization — Established 1946

COLLECTIONS • DATA PROCESSING • MANAGEMENT •

All Third Party Claims Processed

Home Office

76 Pine Street Freeport, N.Y. 11520

I.A.R.S. EDUCATIONAL MEMBERSHIP FOR ALL STUDENTS IN ANESTHESIA TRAINING PROGRAMS

Two-year, one-half price membership, including subscription to ANESTHESIA and ANALGESIA . . . Current Researches.

Application forms available from Cleveland business office. Certification by Program Director required.

This valve makes no difference-except to the atmosphere

Whatever your anaesthesia equipment, so long as it has a BS or ISO standard breathing circuit, there's a place for the new anti-pollution valve – the first element in Medishield's complete theatre pollution control system.

It uses the same well-proven spring and disc principle as your existing valve (but offers less resistance); it introduces no new controls; demands nothing new of the anaesthetist; changes nothing except the theatre conditions.

The swivel-head nozzle permits convenient positioning and with the two metre flexible hose attached conducts anaesthetic pollutants to floor level. Using the new Medishield pollution control system currently being developed it will be possible to extend the valve for remote venting to atmosphere.

Medishield

BOC Medishield (Harlow) Ltd
Elizabeth Way
Harlow, Essex
CM19 5AB
Telephone: Harlow (0279) 29692
Telex: 81497

In USA: Harris Lake Inc In Canada: Medishield Products Ltd

Please send me details of the anti-pollution valve/ pollution control system:

Name_____

Position_____

Hospital_____

Address_____

ANA

Anaesthesia

The official journal of the Association of Anaesthetists of Great Britain and Ireland

Contents: Anaesthesia, vol. 31, no. 2, March 1976

EDITORIAL 167

ORIGINAL ARTICLES

Morbidity following dental extraction: a comparative survey 171
V. M. J. Muir, M. Leonard & E. Haddaway

Day stay anaesthesia. A follow-up of day patients undergoing dental operations under general anaesthesia with endotracheal anaesthesia 181
B. L. Smith & P. N. Young

General anaesthesia for the mentally handicapped 190
A. W. Diamond & D. F. Cochrane

Cardiovascular effects of Althesin: changes in systolic time intervals and peripheral tissue blood flow 195
A. Aronski, A. Kubler, A. Majda & M. Jankowska

Respiratory effects of 'lissive' anaesthesia using gallamine 200
D. W. R. MacFarlane, J. W. Downing & M. C. Mahomedy

Anaesthetic induction for Caesarean section with propanidid 205
M. C. Mahomedy, J. W. Downing, D. E. Jeal & A. J. Coleman

The use of AH8165 for Caesarean section 212
R. D. Cane & D. M. Sinclair

Anticholinergic actions of steroid muscle relaxants 215
J. M. Baden

Pancuronium binding by serum proteins 219
J. M. Thompson

REVIEW ARTICLE

Carcinoid syndrome: its relevance to the anaesthetist 228
R. A. Mason & P. A. Steane

CASE REPORT Anaesthesia for a patient with carcinoid syndrome *R. A. Mason & P. A. Steane* 243

APPARATUS The Bain anaesthetic system *J. D. Henville & A. P. Adams* 247; Co-axial breathing circuit and scavenging valve *J. D. Henville & A. P. Adams* 257; Theatre pollution control *J. A. Lack* 259; Apparatus for emergency intubation in laryngeal obstruction *C. T. B. Allen* 263; Valve control for venturi ventilation *A. J. Asbury* 268

THOUGHTS ON IMMEDIATE CARE Immediate treatment of heatstroke *D. Hamilton* 270

HISTORICAL NOTE Poiseille and his law *J. Pfitzner* 273

FORUM General anaesthesia with propanidid infusion for suspension microlaryngoscopy without intubation *G. Macavero, S. Gregoretti & A. Bosatra* 276; Althesin infusion for cardiac catheterisation *J. D. Alderson, J. M. Hampson, P. J. R. Jebson & J. A Thornton* 280

SPECIAL ARTICLE The World Federation of Societies of Anaesthesiologists (W.F.S.A.) *J. S. M. Zorab* 285

CORRESPONDENCE List of contents 293

MEMORANDUM FROM STANDING SUB-COMMITTEE ON SAFETY IN ANAESTHESIA Oxygen supply pressure failure warning and protection devices 316

Système International (SI) conversion tables 319

NEWS AND NOTICES New Year honours 323; Obituaries 323; Association of Anaesthetists 323; Anaesthetists' sub-committee of CCHMS 330; Junior Anaesthetists 331; Faculty RCSEng. 333; Faculty RCSI 335; Royal Society of Medicine 336; Home news 337; National and local events 341; International news 344; International congress calendar 348

BOOK REVIEWS 304 AUDIOVISUAL REVIEWS 315 STOP PRESS 350

COURSES IN ANAESTHESIA 351 ANAESTHETIC LITERATURE 362

Published nine times a year at £20.00 (U.K.), £24.00 (overseas), $67.50 (U.S.A. and Canada) per annum, post free. Subscriptions and requests for specimen copies should be sent to Blackwell Scientific Publications, P.O. Box 88, Oxford, England.

Blackwell Scientific Publications

Oxford London Edinburgh Melbourne

INTRODUCING

the PSI 5000 Recorder

MEASURES & RECORDS

ECG • PULSE •
VITAL PRESSURES

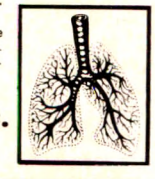
- ARTERIAL
- VENOUS
- INTERCRANIAL
- PULMONARY WEDGE

WHEN VERSATILITY COUNTS

BATTERY OPERATION, VARIABLE AMPLITUDES
VARIABLE SPEEDS AND TREND - 2.5 to 50 mm/Sec.

Whenever precise permanent copies are essential.

The PSI 5000 Recorder is a portable, battery operated, self-contained unit for use in most heart, lung, and blood pressure measurements. The PSI 5000 meets AHA specifications for electrocardiography, assuring superior performance in any application requiring high frequency response. The pen stylus is held in a stress-free mount on a titanium arm to provide exceptional life. It is capable of sustaining up to 1000 G's acceleration. A fully charged battery will provide up to four hours continuous operation.



Pulmonary Specialties, Inc.

231 COMMERCE DRIVE, LARGO, FLORIDA 33540 • TELEPHONE (813) 585-4772

Non-conductive blood pressure cuffs . . . in color!

Color-code your departments! Dupaco offers high quality non-conductive blood pressure cuffs in red, blue denim, paisley or plaid. Monogramming available up to 20 stitched letters, with department or individual's name.

Stain resistant, washable, with velcro attaching strips for Dupaco Diasyst.® Sizes listed below. For more information write: Dupaco Inc., P.O. Box 98, San Marcos, CA 92069.

Adult	5¾" x 22"
Medium Adult	5" x 17¾"
Child	3¾" x 14½"
Infant	2¾" x 11½"

DUPACO
INCORPORATED

INDEX OF ADVERTISERS

Air Products and Chemicals, Inc.—*Anesthesia Control Center* ..... (59), (60), (61), (62)

Air Products and Chemicals, Inc.—*Trace Gas Monitor* ..... (72)

Allergan Pharmaceuticals—*Lacri-Lube*® ..... (57)

Anaesthesia Magazine ..... (67)

Applied Medical Research Corporation—*Dinamap* ..... (47)

Ayerst Laboratories—*Fluothane*® ..... (6), (7), (8)

Burroughs Wellcome Co.—*Anectine*® ..... (64), (65)

Cavitron/KDC Medical Sales—*Gas Analyzer* ..... (33)

Datascope Corp.—*Monitors* ..... (43)

Dupaco, Inc.—*Blood Pressure Cuffs* ..... (27)

Dupaco, Inc.—*Opti-Gard*(TM) ..... (51)

Dupaco, Inc.—*Non Conductive Blood Pressure Cuffs* ..... (68)

J. H. Emerson Company—*Emerson Relaxaid*(TM) ..... (31)

Endo Laboratories—*Narcan*® ..... (12), (13), (14)

Fenwal Laboratories—*Operating Room System* ..... (19, (20), (21), (22)

Harris-Lake, Inc.—*Laryngoscopes* ..... (2)

McNeil Laboratories, Inc.—*Innovar*® ..... (49), (50)

McNeil Laboratories, Inc.—*Sublimaze*® ..... (28), (29), (30)

Medical and Industrial Equipment Div., Claudius Ash, Inc.—*Jackson-Rees T-Piece* ..... (26)

Medical Management Company—*Management Services* ..... (66)

Medishield Corporation Ltd.—*Anti-Pollution Valve* ..... (66)

Medsonics, Inc.—*Versatone*(TM) *Doppler* ..... (63)

Merck, Sharp & Dohme—*Aramine*® ..... (23)

National Catheter Corp.—*Catheters* ..... (24), (25)

North American Drager—*Narkomed Anesthesia Machine* ..... (9)

Ohio Medical Products—*Ethrane*® ..... (16), (17), (18)

O'Neal, Jones & Feldman, Inc.—*Antilirium* ..... (58)

Organon, Inc.—*Pavulon*® ..... (39), (40), (41)

Pennwalt Corp.—*Nesacaine*® ..... (10), (11)

Pfizer Laboratories—*Vistaril*® *I.M.* ..... (44), (45), (46)

Pharmaseal Laboratories—*Anesthesia Trays* ..... (70), (71)

Professional Instruments Co.—*Peripheral Nerve Stimulator* ..... (51)

Pulmonary Specialties, Inc.—*PSI 5000 Recorder* ..... (68)

A. H. Robins Co., Inc.—*Dopram*® ..... (52), (53)

Schuemann Labs. (Rals Div.)—*Rals Power Unit* ..... (27)

Tektronix, Inc.—*Portable Patient Monitor* ..... (32)

When to use the word Phär′mȧ·sēal.

For components, features, "performance" in single-use anesthesia trays, just say the word.

The trays you've counted on from the start now offer you even more to go on.

Back in 1963 we introduced the world's first single-use, regional anesthesia trays.

Today, with a record of safe performance difficult to equal, we offer you an even wider selection of components and features—just as difficult to match—in spinal, caudal and epidural trays.

All with our all-new spinal needle. The needle that's been called the cleanest spinal needle yet. The one with a cannula with almost uncanny smoothness, a cartridge pack with an exceptional point protector, a matched-ground point, metal hub and more.

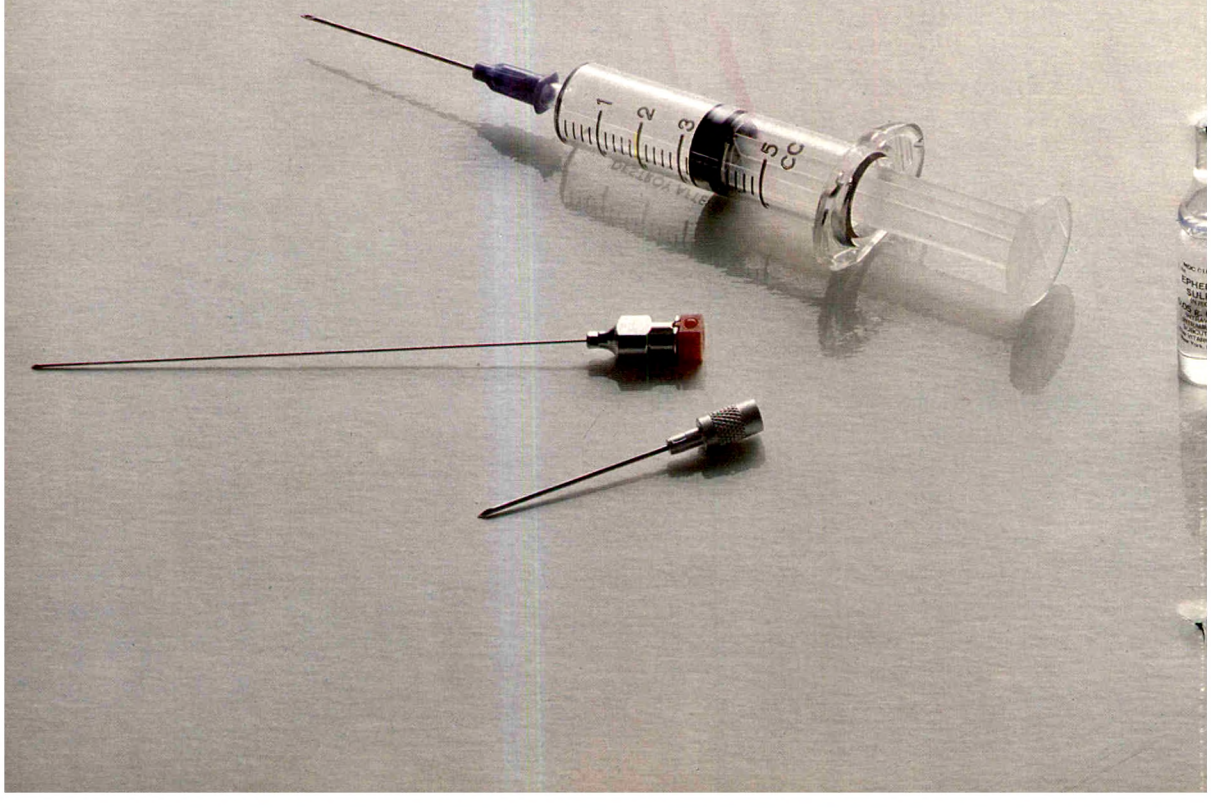
Trays that offer you a new fenestrated drape with its own adhesive tabs.

A large, moisture-resistant hospital wrap with a new "wrinkle" for better procedure.

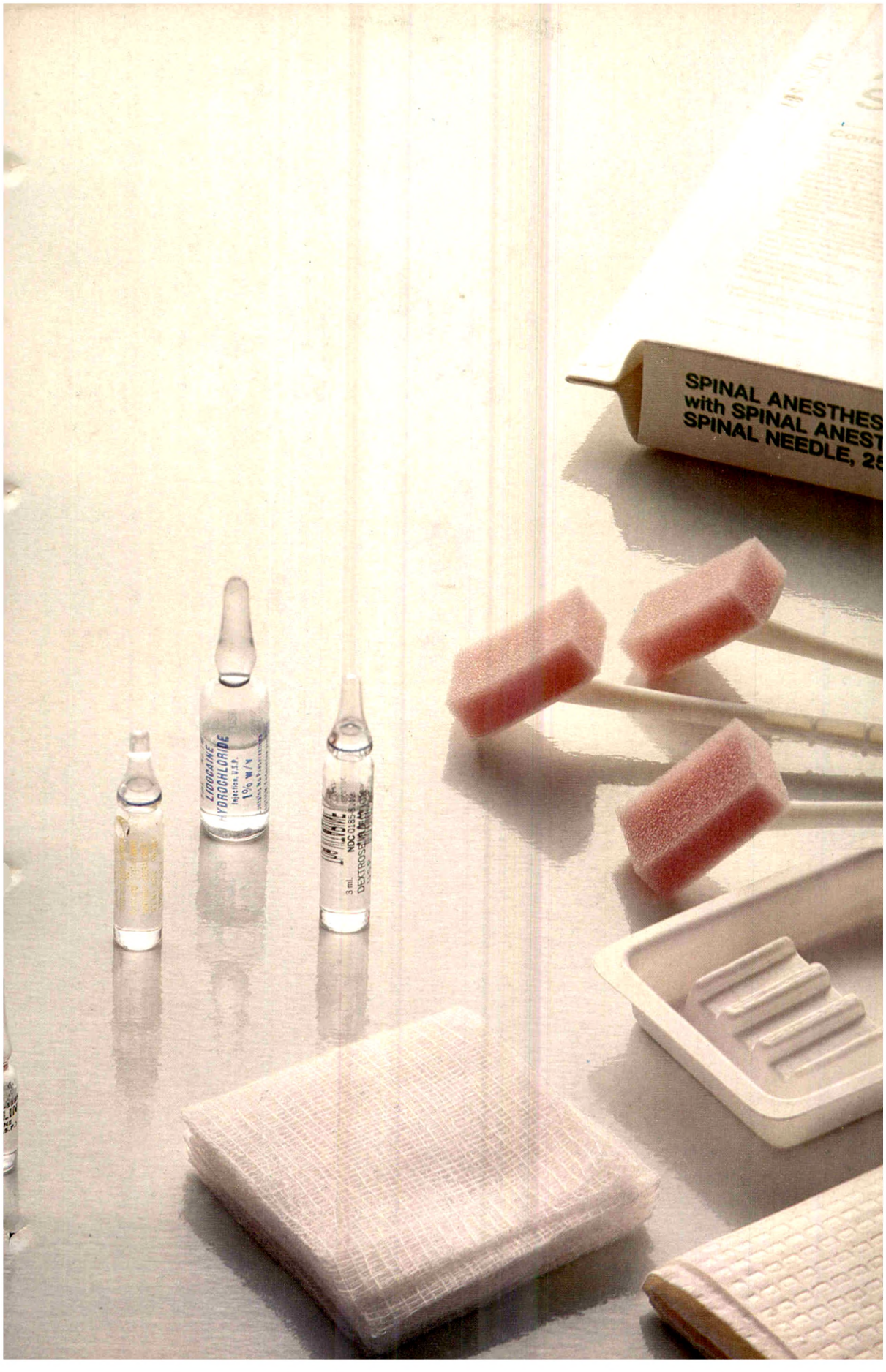
Plus, a specially designed introducer needle, a clear 5-cc. Stylex® syringe, a unique aseptic transfer carton...and a variety of other first-quality components and drugs.

But see for yourself what we're talking about. See the trays with performance you can count on. For samples, just call or write.

You know the word to use.



O.R./ANESTHESIA PRODUCTS BY
PHARMASEAL
GLENDALE, CALIFORNIA 91201


SPINAL ANESTHES
with SPINAL ANEST
SPINAL NEEDLE, 25
LIDOCAINE
HYDROCHLORIDE
Injection, U.S.P.
1% W/V
3 mL
NDC 0183-8
DEXTROSE

If You're Confused About O.R. Pollution, **Cut It Out.**

Get a compilation of data on the problems of trace anesthetic gas and OR pollution control. Send for our Positive Response Program.

Besides reports and studies to help you put the problem in perspective, our "PRP" plan of action provides an up-to-date look at our products which help you detect and scavenge trace gas in your OR. Key to our program is the Foregger 410 N_2O Trace Gas Monitor, a basic requirement for any efficient trace gas monitoring program. It's designed to provide rapid and continuous sampling of the OR air you breathe.

The machine has two sensing modes—Monitor (0-100 ppm) and Leak Test (0-1,000 ppm). The first mode continuously monitors the ambient air through the gas inlet of the machine. The second permits probing of local concentrations and sounds a repetitive burst alarm as the gas concentration increases.

In short, the Foregger 410 N_2O Trace Gas Monitor is a logical first step in solving your OR pollution problem. And there's more. The Scaveng-OR™ Gas Evacuator System, the Protect-OR™ Filter, Wall Suction Systems, and Air-CARE™ Preventive Maintenance Service.

Based on current data, it's likely that routine monitoring of pollution levels and scavenging of waste anesthetic gases will soon be standard Operating Room procedure. We're ready to help you now.

Fill out this ad coupon or ask our Representative for a Foregger PRP Folder. You'll get the problem in perspective and a plan of action to help correct it.

Air Products
FOREGGER

Yes, I am interested in minimizing my O.R. pollution problem. And I want a plan to help correct it. Send me your plan of action.

(Please print or type)

Name _____ Title _____

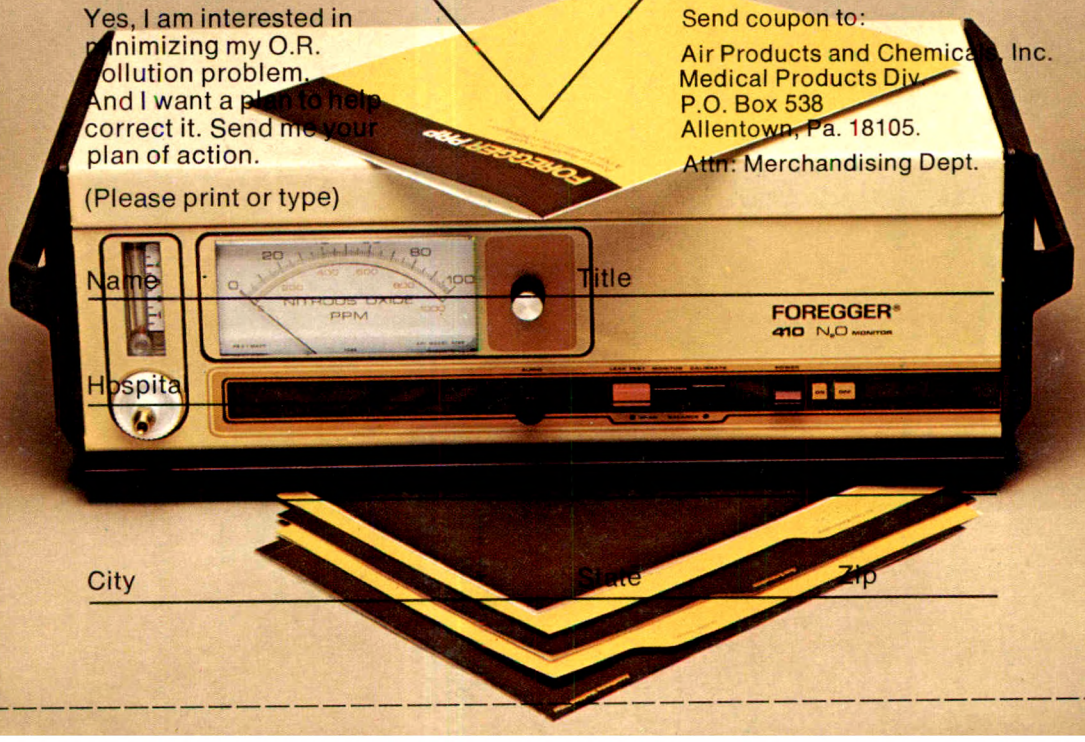
Hospital _____

City _____ State _____ Zip _____

Send coupon to:

Air Products and Chemicals, Inc.
Medical Products Div.
P.O. Box 538
Allentown, Pa. 18105.

Attn: Merchandising Dept.



Ane.
22.3.77

Anesthesia AND Analgesia

.....CURRENT RESEARCHES

On the History of Ideas in Anaesthesia ..... Page 467

Changes in Blood Chemistries Following Prolonged Enflurane Anesthesia ..... Page 547

Table of Contents ..... Page (4)

Oldest Publication in the Specialty - Established 1922

Journal of the International Anesthesia Research Society

Volume 55, No. 4 July-August, 1976

51st Congress

Hollywood, Florida - March 6-10, 1977

Harlake® laryngoscopes

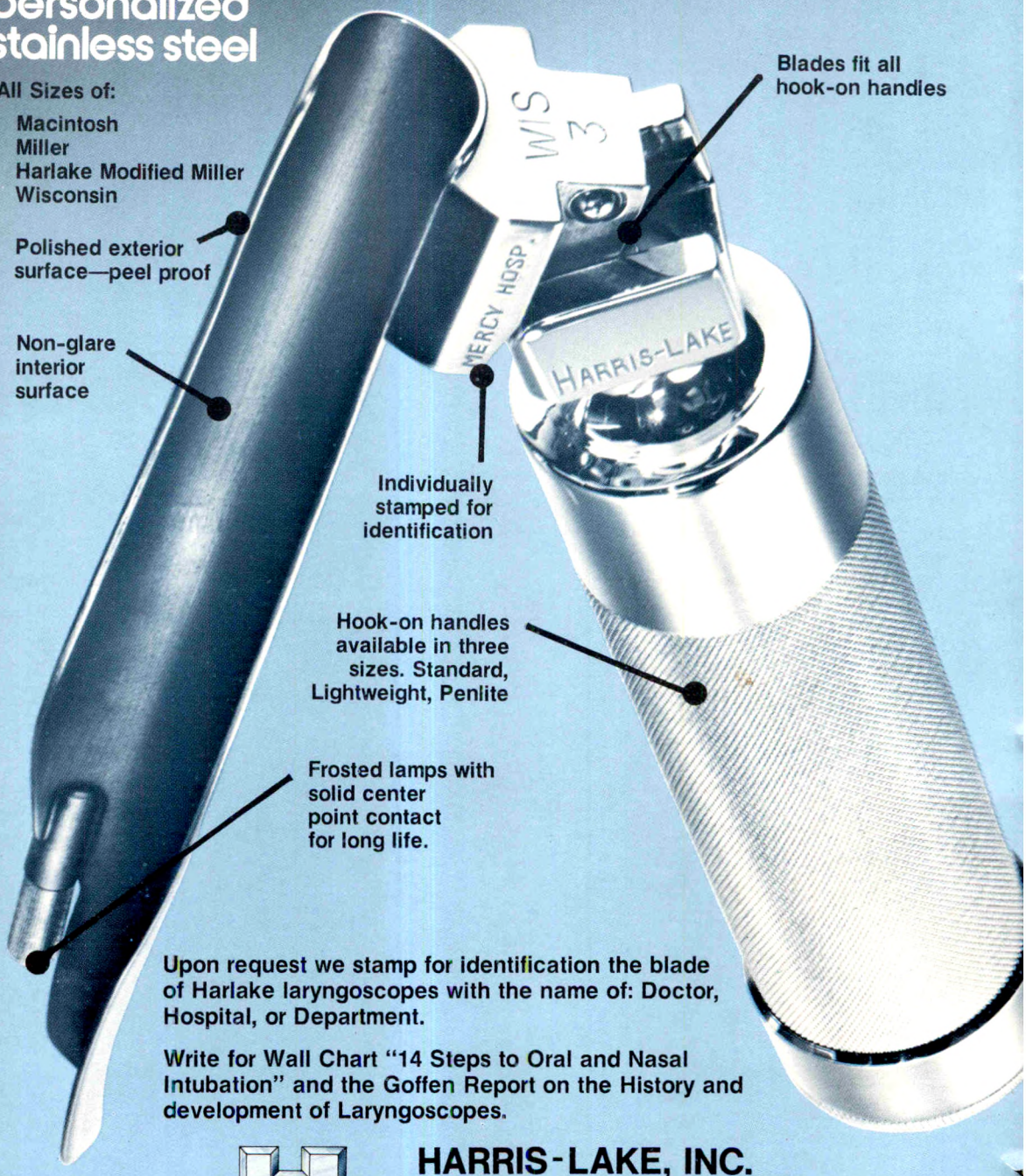
personalized stainless steel

All Sizes of:

Macintosh
Miller
Harlake Modified Miller
Wisconsin

Polished exterior surface—peel proof

Non-glare interior surface



Blades fit all hook-on handles

Individually stamped for identification

Hook-on handles available in three sizes. Standard, Lightweight, Penlite

Frosted lamps with solid center point contact for long life.

Upon request we stamp for identification the blade of Harlake laryngoscopes with the name of: Doctor, Hospital, or Department.

Write for Wall Chart "14 Steps to Oral and Nasal Intubation" and the Goffen Report on the History and development of Laryngoscopes.

HARRIS-LAKE, INC.
10910 Briggs Road, Cleveland, Ohio 44111
Telephone (216) 251-8870
Telex: 98-5454

A Medishield Company Medishield

Anesthesia AND Analgesia ...CURRENT RESEARCHES

JOURNAL OF THE INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

3645 Warrensville Center Road • Cleveland, Ohio, U.S.A. 44122 • Telephones: (216) 295-1124, 295-1130

EDITORIAL BOARD

Editor: T. H. Seldon, M.D., Rochester, Minnesota

Associate Editors:
John T. Martin, M.D., Toledo, Ohio
Emerson A. Moffitt, M.D., Halifax, Nova Scotia
Dean H. Morrow, M.D., Houston, Texas
Edwin S. Munson, M.D., Gainesville, Florida
Robert K. Stoelting, M.D., Indianapolis, Indiana

Contributing Editors:
Douglas B. Craig, M.D., Winnipeg, Manitoba
E. Paul Didier, M.D., Rochester, Minnesota
Ronald W. Dunbar, M.D., Atlanta, Georgia
Leonard C. Jenkins, M.D., Vancouver, British Columbia
David E. Longnecker, M.D., Charlottesville, Virginia
John J. Savarese, M.D., Boston, Massachusetts
N. Ty Smith, M.D., San Diego, California

ANESTHESIA AND ANALGESIA . . . Current Researches is published bimonthly by the International Anesthesia Research Society, a non-profit scientific and educational corporation of the state of Ohio. Members of the Board of Trustees of the Society are: Kenneth K. Keown, M.D., John T. Martin, M.D., Emerson A. Moffitt, M.D., Dean H. Morrow, M.D., Edwin S. Munson, M.D., B. B. Sankey, M.D., T. H. Seldon, M.D., Robert K. Stoelting, M.D. Emeritus Trustees are: Paul R. Dumke, M.D., Morris J. Nicholson, M.D.

EDITORIAL CORRESPONDENCE and manuscripts should be addressed to: **T. H. Seldon, M.D., Editor, Kahler East—Suite C, Rochester, Minnesota 55901, U.S.A. Telephone: (507) 288-8655.** (See "A Guide for Authors" for information concerning manuscript preparation.) Original articles accepted for publication, or papers presented at the Society's annual scientific meetings which are subsequently published in this Journal become the property of the International Anesthesia Research Society, publisher. Reproduction in whole or in part is not permitted except by written consent of the publisher and the author.

BUSINESS CORRESPONDENCE, including subscription and membership payments, single issue purchases, change of address notices, requests for membership applications, should be sent to: **B. B. Sankey, M.D., Executive Secretary and Business Manager, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122. Telephones: (216) 295-1124, 295-1130.**

SUBSCRIPTION RATE: $25.00 per year (6 issues), including postage.

MEMBERSHIP DUES: $25.00 per year, includes a subscription to the Journal. **Membership** available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine or other disciplines who are engaged either in active clinical practice of or research in anesthesiology. **Associate Membership** available to individuals certified, licensed or accredited in anesthesia-related professions (CRNA, ARIT, Physician Assistant). **Educational Membership** (two years for $25.00) available to interns, residents, students in nurse anesthesia and related training programs.

SINGLE ISSUES: $4.50 each for years beginning 1970; $3.00 for years 1954-1969; $2.00 for years 1928-1953. (See "Back Issues Available" or write to Cleveland business office for listing.)

REPRINTS: For single copies, write directly to senior author at address listed on title page. Quantity orders (minimum 100) processed through Cleveland business office, prices on request.

MAILING DATES: Journals mailed 25th of January, March, May, July, September and November. Second Class postage paid at Cleveland, Ohio.

CHANGE OF ADDRESS NOTICES: Send to Cleveland business office by first day of the above months to ensure correct addressing of Journals. Replacement copies of missing Journals will be furnished without charge only if original copy is returned by post office as undeliverable.

ADVERTISING: Rate sheets, including advertising clearance procedure, available from national advertising representative: Charles B. Slack, Inc., 6900 Grove Road, Thorofare, New Jersey 08086—Telephone: (609) 848-1000. Orders, contracts, reproduction materials, set copy and classified ad copy should be sent only to Cleveland office.

©1976, International Anesthesia Research Society.

Contents

Volume 55 July-August, 1976 Number 4

SCIENTIFIC ARTICLES

ON THE HISTORY OF IDEAS IN ANAESTHESIA—Vandam 467

INFLUENCE OF PANCURONIUM ON POTASSIUM EFFLUX PRODUCED BY SUCCINYLCHOLINE—Konchigeri and Tay 474

PHYSOSTIGMINE REVERSAL OF SEDATION IN PARTURIENTS—Smith, Clark, Stephens, Sherman and Hyde 478

RESPIRATORY DISTRESS WITH LEFT AORTIC ARCH, RIGHT DESCENDING AORTA, AND RIGHT LIGAMENTUM ARTERIOSUM: A CASE REPORT—Moorthy, Franken, LoSasso and King 481

INFLUENCE OF PANCURONIUM OR d-TUBOCURARINE ON CIRCULATORY RESPONSES DURING THIAMYLAL-N_2O-HALOTHANE ANESTHESIA—Stoelting 485

SPINAL ANESTHESIA: BUPIVACAINE VERSUS TETRACAINE—Pflug, Aasheim and Beck 489

ANAPHYLAXIS: ETIOLOGY AND GUIDELINES FOR MANAGEMENT—Morrow and Luther 493

NEUROMUSCULAR BLOCKING EFFECTS OF AMINOGLYCOSIDE ANTIBIOTICS ON FAST- AND SLOW-CONTRACTING MUSCLES OF THE CAT—Adams, Mathew, Teske and Mercer 500

"ACUPUNCTURE ANESTHESIA"—A CLINICAL STUDY—Modell, Lee, Bingham, Greer and Habal 508

PERIOPERATIVE AWARENESS AND RECALL—Eisele, Weinreich and Bartle 513

SEVERE HYPERTENSION IN A CHILD WITH WILMS' TUMOR: A CASE REPORT—Cobb and Vaughan 519

CLINICAL EVALUATION OF INJECTABLE LORAZEPAM AS A PREMEDICANT: THE EFFECT ON RECALL—Blitt, Petty, W. Wright and B. Wright 522

INTRAOPERATIVE AWAKENING FOR EARLY RECOGNITION OF POSSIBLE NEUROLOGIC SEQUELAE DURING HARRINGTON-ROD SPINAL FUSION—Sudhir, Smith, Hall and Hansen 526

FLUROXENE (2,2,2-TRIFLUOROETHYL VINYL ETHER) TOXICITY: A CHEMICAL ASPECT—Harrison, Ivanetich, Kaminsky and Halsey 529

THOUGHTS ABOUT MEDICAL WRITING. XXXVI. WRITING AN EDITORIAL—Roland 534

ELECTROANESTHESIA (EA) STUDIES: EA PRODUCED BY STIMULATION OF SENSORY NERVES OF THE SCALP IN RHESUS MONKEYS—Kano, Cowan and Smith 536

POST-THORACOTOMY INTERCOSTAL BLOCK: COMPARISON OF ITS EFFECTS ON PULMONARY FUNCTION WITH THOSE OF INTRAMUSCULAR MEPERIDINE—Faust and Nauss 542

CHANGES IN BLOOD CHEMISTRIES FOLLOWING PROLONGED ENFLURANE ANESTHESIA—Eger, Calverley and Smith 547

SPINAL ANESTHESIA FOR LUMBAR DISC SURGERY: REVIEW OF 576 OPERATIONS—Silver, Dunsmore and Dickson 550

HYPOXEMIA AND HYPOCARBIA FOLLOWING INTERMITTENT POSITIVE-PRESSURE BREATHING—Wright, Foley, Downs and Hodges 555

Anesthesia AND Analgesia . . . Current Researches

SCIENTIFIC ARTICLES—July-August, 1976 (Continued)

CARDIOVASCULAR AND RESPIRATORY EFFECTS OF ISOPROTERENOL BEFORE AND AFTER ARTIFICIAL HEART IMPLANTATION—Liu, Stanley, Isern-Amaral, Ward, Lunn, Gentry and Atwood 560

THE LOCAL ANESTHETIC ACTIVITY OF TETRODOTOXIN ALONE AND IN COMBINATION WITH VASOCONSTRICTORS AND LOCAL ANESTHETICS—Adams, Blair and Takman 568

A DOSAGE NOMOGRAM FOR SODIUM NITROPRUSSIDE-INDUCED HYPOTENSION UNDER ANESTHESIA—Lawson, Thompson, Nelson, Flacke and Seifen 574

"AN' HO, HO, BABY, TAKE A WHIFF ON ME:" LA DAMA BLANCA COCAINE IN CURRENT PERSPECTIVE—Gay, Inaba, Rappolt, Gushue and Perkner 582

CASE HISTORY NUMBER 91: SUSTAINED HIGH INSPIRED Po_2 WITHOUT TOXIC SEQUELAE—Gibbs, Moorthy and LoSasso 588

BRIEF REPORTS

PREVENTION OF HYPOTHERMIA DURING CYSTOSCOPY IN NEONATES—Meyers and Oh 592

ESTIMATION OF ANESTHETIC SOLUBILITY IN BLOOD—Feingold 593

SIGNIFICANCE OF Pco_2 WITHIN LOW-PRESSURE ENDOTRACHEAL TUBE CUFFS—Levesque 595

SHEARING HAZARD OF INTRA-ARTERIAL TEFLON CATHETERS—Talmage 597

EVALUATION OF LARYNX AND TRACHEA BY XERORADIOGRAPHY—Moorthy, LoSasso, King and Franken 598

PNEUMATOCELE OF THE LARYNX: A COMPLICATION OF PERCUTANEOUS TRANSTRACHEAL VENTILATION—Carden, Calcaterra and Lechtman 600

ACUTE ETHANOL INTOXICATION AND ITS PROLONGED EFFECT ON A FULL-TERM NEONATE—Kim and Hodgkinson 602

FEATURES

People and Places ..... (19)
Correction 473
We Salute—Edmond I. Eger, II, M.D. 604
Correspondence:
Nonflammable Germicides or Detergents—DelPizzo 606
Insect-sting Kit—Frazier 606
Editor's Choice 607
The Physician and The Law 611
Questions and Answers 613
Scientific Articles, Next Issue ..... (31)
A Guide for Authors ..... (32)
Classified Advertising ..... (39)
Something New ..... (55)
Index of Advertisers ..... (65)

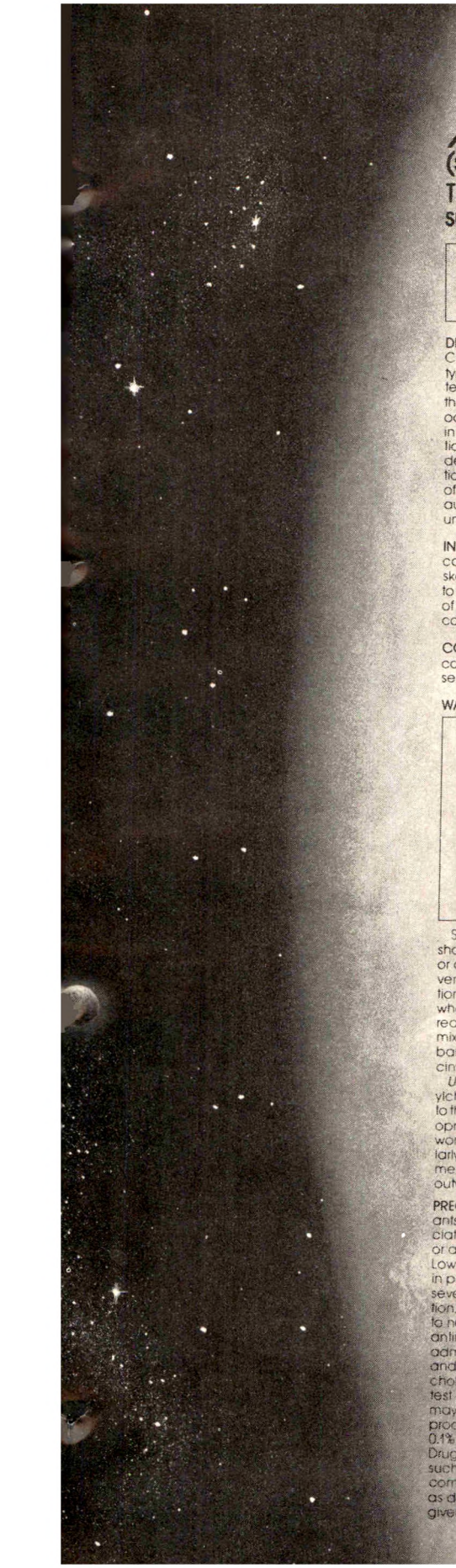
ANECTINE®
(succinylcholine chloride)
For controlled muscle relaxation adjunctive to anesthesia:

FLO-PACK® for prolonged relaxation

- instant-mix sterile powder interfaces with all major parenteral systems (vacuum or nonvacuum)
- each unit complete—no needle or syringe needed
- retains potency indefinitely
- no refrigeration required
- unbreakable, sterile plastic injection units of 500 and 1,000 mg

INJECTION for short-term relaxation

- a product of choice for intubation and other short procedures
- unique square bottle and bright yellow label for positive identification
- ready for immediate use
- 20 mg per cc . . . in 10 cc multidose vials
- flip-top cap for easy opening
- single or multiple use



ANECTINE®
(succinylcholine chloride)
THE LONG AND SHORT of surgical muscle relaxation

THIS DRUG SHOULD BE USED ONLY BY INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS AND HAZARDS.

DESCRIPTION: Anectine brand Succinylcholine Chloride is an ultra short-acting depolarizing type muscle relaxant. Chemically it is a di-quaternary base consisting of the di-chloride salt of the di-choline ester of succinic acid. It is a white, odorless, slightly bitter powder and very soluble in water. The drug is unstable with alkaline solutions, but relatively stable in acid solutions depending upon the concentration of the solution and the storage temperature. While solutions of succinylcholine chloride are sterilized by autoclaving, they should, nevertheless, be stored under refrigeration to preserve their potency.

INDICATIONS: Succinylcholine chloride is indicated as an adjunct to anesthesia to induce skeletal muscle relaxation. It may be employed to reduce the intensity of muscle contractions of pharmacologically or electrically induced convulsions.

CONTRAINDICATIONS: Succinylcholine is contraindicated for persons with a known hypersensitivity to the drug.

WARNINGS:

WARNING: SUCCINYLCHOLINE SHOULD BE USED ONLY BY THOSE SKILLED IN THE MANAGEMENT OF ARTIFICIAL RESPIRATION AND ONLY WHEN FACILITIES ARE INSTANTLY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND FOR PROVIDING ADEQUATE VENTILATION OF THE PATIENT, INCLUDING THE ADMINISTRATION OF OXYGEN UNDER POSITIVE PRESSURE AND THE ELIMINATION OF CARBON DIOXIDE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR TO CONTROL RESPIRATION.

Succinylcholine should not be mixed with short-acting barbiturates in the same syringe, or administered simultaneously during intravenous infusion through the same needle. Solutions of succinylcholine have an acid pH whereas those of barbiturates are alkaline in reaction. Depending upon the resultant pH of a mixture of solutions of these drugs, either free barbituric acid may be precipitated or succinylcholine hydrolyzed.

Usage in Pregnancy. The safe use of succinylcholine has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

PRECAUTIONS: Low levels of, or abnormal variants of plasma cholinesterase may be associated with prolonged respiratory depression or apnea following the use of succinylcholine. Low levels of plasma cholinesterase may occur in patients with severe liver disease or cirrhosis, severe anemia, malnutrition, severe dehydration, changes in body temperature, exposure to neurotoxic insecticides or those receiving antimalarial drugs. Succinylcholine should be administered with extreme care to such patients and dosage should be minimal. If low plasma cholinesterase activity is suspected, a small test dose of from 5 to 10 mg of succinylcholine may be administered, or relaxation may be produced by the cautious administration of a 0.1% solution of the drug by intravenous drip. Drugs which either inhibit plasma cholinesterase, such as neostigmine or phospholine iodide, or compete with succinylcholine for the enzyme, as does intravenous procaine, should not be given concurrently with succinylcholine.

Succinylcholine should be administered with great caution to patients with severe burns, those recovering from severe trauma, those suffering from electrolyte imbalance, those receiving quinidine, those who have been digitalized recently or who may have digitalis toxicity as serious cardiac arrhythmias or cardiac arrest may result. Great caution should be observed also in patients with pre-existing hyperkalemia or who are paraplegic, have suffered spinal neuraxis injury, or have degenerative or dystrophic neuromuscular disease, as such patients tend to become severely hyperkalemic when succinylcholine is given.

When succinylcholine is given over a prolonged period of time, the characteristic depolarization block of the myoneural junction may change to a non-depolarizing block which results in prolonged respiratory depression or apnea. Under such circumstances, small repeated doses of neostigmine may possibly act as an antagonist. A peripheral nerve stimulator (e.g., the Wellcome Peripheral Nerve Stimulator) may be used to ascertain the type of neuromuscular blockade. If a depolarization block is present both fast (tetanic) and slow (twitch) rates of nerve stimulation are well sustained, and post-tetanic facilitation is absent. If a non-depolarizing block is present there is post-tetanic facilitation and "fade" of successive stimuli on both fast (tetanic) and slow (twitch) rates of nerve stimulation.

Succinylcholine should be used with caution during ocular surgery and in patients with glaucoma. The drug should be employed with caution in patients with fractures or muscle spasm as the muscle fasciculations may cause additional trauma. Muscle fasciculations and hyperkalemia may be reduced by administering a small dose of a non-depolarizing relaxant. If other relaxants are to be used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered.

During the past few years, reports have called attention to a fulminant syndrome, malignant hyperthermia, observed during anesthesia. Its etiology is not fully understood. Malignant hyperthermia occurs in genetically prone individuals of all ages and both sexes receiving potent anesthetics such as halothane, methoxyfluothane, cyclopropane and diethyl ether. It appears to develop irrespective of the concomitant use of a muscle relaxant, but may be triggered by succinylcholine. Because of the seriousness of this syndrome and the need for early effective treatment of the patient, it is suggested that the continuous monitoring of the temperature will serve as an aid to the early recognition of malignant hyperthermia.

ADVERSE REACTIONS: Adverse reactions consist primarily of an extension of the drug's pharmacological actions. Profound and prolonged muscle relaxation may occur, resulting in respiratory depression to the point of apnea. Hypersensitivity to the drug may exist in rare instances.

The following adverse reactions have been reported: bradycardia, tachycardia, hypertension, hypotension, arrhythmias, cardiac arrest, prolonged respiratory depression or apnea, hyperthermia, increased intraocular pressure, muscle fasciculation, postoperative muscle pain, myoglobinemia and excessive salivation.

MANAGEMENT OF ADVERSE REACTIONS: Apnea or prolonged muscle paralysis should be treated with controlled respiration.

The use of neostigmine to reverse a non-depolarization block is a medical decision which must be made upon the basis of the individual clinical pharmacology and the experience and judgment of the clinician. When neostigmine is used atropine should also be administered.

SUPPLIED: Injection, Multi-dose vials, 20 mg. cc, 10 cc, boxes of 12 vials. Flo-Pack® Sterile Powder 500 mg and 1,000 mg, boxes of 12.

Complete literature available on request from Professional Services Dept. PML.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

Selected cases for Ketalar® (ketamine HCl injection)

(and a caution)

There are certain situations where the advantages of Ketalar suggest its serious consideration.

Four such hypothetical situations are detailed here. A fifth hypothetical case illustrates a situation in which Ketalar probably should be used only with caution.

Geriatric surgical procedure

Ketalar offers advantages in minor rectal surgery on elderly patients. When properly administered, Ketalar usually does not depress the patient's blood pressure or pulse rate, which can be a distinct advantage with any patient who is likely to develop hypotension. Further, emergence reactions normally are not a problem with patients in the older age group (over 65).

Severely burned patients

Patients with severe burns—and particularly children—are often excellent cases for Ketalar. In children, Ketalar offers rapid surgical anesthesia (generally within three to four minutes) at a range of 9 to 13 mg/kg, with the effect lasting from 12 to 25 minutes (the time intervals are for IM, not IV). Intramuscular administration avoids the possible difficulty in locating the vein in burn patients (particularly helpful in children where the veins are small). IM administration is also convenient and effective for repeated short-term anesthesia for such procedures as changing burn dressings, and skin grafts.

Manipulative diagnostic procedure

Ketalar facilitates diagnostic procedures in which the patient must be moved freely, and in which the maintenance of unaided respiration is essential. The pneumoencephalogram is an example. Once anesthesia is established, the patient can be transferred from a supine to an upright, supported position with ease since Ketalar maintains adequate unaided respiration, and there is minimal relaxation of the skeletal muscles.

Emergency room treatment

A good case for Ketalar can be made for use in accident victims with unknown medical histories brought to the emergency room. In the absence of positive medical history, Ketalar can be a useful agent because of its wide margin of safety. Consideration should be given to the effects of a significant increase in blood pressure, hypersensitivity to the drug, and an elevation in cerebrospinal fluid pressure. Ketalar also provides the benefit of rapid onset, and decreases the chance of aspiration because of active laryngeal-pharyngeal reflexes.

A caution:

Caution should be exercised when administering Ketalar to patients who are known to be alcoholics or who are acutely alcohol-intoxicated as such patients may be prone to untoward reactions.

Please see following page for brief summary of prescribing information.

advancement in anesthesiology
Ketalar
(Ketamine HCl injection)
Parke-Davis

advancement in anesthesiology

Ketalar

(Ketamine HCl injection)

Brief summary of prescribing information.

SPECIAL NOTE

EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12% OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT, DREAMLIKE STATES, VIVID IMAGERY, HALLUCINATIONS, AND EMERGENCE DELIRIUM. IN SOME CASES, THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY LASTS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETALAR.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE YOUNG (15 YEARS OF AGE OR LESS) AND ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY.

THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS. IN ADDITION, THE USE OF A SMALL HYPNOTIC DOSE OF A SHORT-ACTING OR ULTRASHORT-ACTING BARBITURATE MAY BE REQUIRED TO TERMINATE A SEVERE EMERGENCE REACTION. THE INCIDENCE OF EMERGENCE REACTIONS IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

WHEN KETALAR IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

INDICATIONS

Ketalar (ketamine HCl injection) is recommended:

1. as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketalar is best suited for short procedures but it can be used, with additional doses, for longer procedures;

2. for the induction of anesthesia prior to the administration of other general anesthetic agents;

3. to supplement low-potency agents, such as nitrous oxide.

CONTRAINDICATIONS

Ketamine hydrochloride is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard and those who have shown hypersensitivity to the drug.

WARNINGS

1. Ketalar should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration.

2. Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.

3. Barbiturates and Ketalar, being chemically incompatible because of precipitate formation, *should not* be injected from the same syringe.

4. Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar.

5. Postoperative confusional states may occur during the recovery period.

6. Respiratory depression may occur with overdosage or too rapid a rate of administration of Ketalar, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

Usage in Pregnancy

Since the safe use in pregnancy, including obstetrics (either vaginal or abdominal delivery), has not been established, such use is not recommended.

PRECAUTIONS

1. Because pharyngeal and laryngeal reflexes are usually active, Ketalar (ketamine HCl injection) should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if Ketalar is used alone. Muscle relaxants, with proper attention to respiration, may be required in both of these instances.

2. Resuscitative equipment should be ready for use.

3. ***The incidence of emergence reactions may be reduced*** if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note).

4. The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced pressor response.

5. In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain.

6. Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.

7. An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure.

ADVERSE REACTIONS

Cardiovascular: Blood pressure and pulse rate are frequently elevated following administration of Ketalar. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.

Respiration: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of Ketalar (ketamine HCl injection). Laryngospasms and other forms of airway obstruction have occurred during Ketalar anesthesia.

Eye: Diplopia and nystagmus have been noted following Ketalar administration. It also may cause a slight elevation in intraocular pressure measurement.

Psychological: (See Special Note).

Neurological: In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures (see Dosage and Administration).

Gastrointestinal: Anorexia, nausea and vomiting have been observed; however this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness (see Dosage and Administration).

General: Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

DOSAGE AND ADMINISTRATION

Preoperative Preparations:

1. While vomiting has been reported following Ketalar administration, airway protection is usually afforded because of active laryngeal-pharyngeal reflexes. However, since these reflexes may also be diminished by supplementary anesthetics or muscle relaxants, the possibility of aspiration must be considered. Ketalar is recommended for use in the patient whose stomach is not empty when, in the judgment of the practitioner, the benefits of the drug outweigh the possible risks.

2. Atropine, scopolamine, or other drying agent should be given at an appropriate interval prior to induction.

Dosage

As with other general anesthetic agents, the individual response to Ketalar (ketamine HCl injection) is somewhat varied depending on the dose, route of administration, and age of patient, so that dosage recommendation cannot be absolutely fixed. The drug should be titrated against the patient's requirements.

Onset and Duration:

Because of rapid induction following the initial intravenous injection, the patient should be in a supported position during administration.

The onset of action of Ketalar (ketamine HCl injection) is rapid; an intravenous dose of 2 mg/kg (1 mg/lb) of body weight usually produces surgical anesthesia within 30 seconds after injection, with the anesthetic effect usually lasting five to ten minutes. If a longer effect is desired, additional increments can be administered intravenously or intramuscularly to maintain anesthesia without producing significant cumulative effects.

Intramuscular doses, from experience primarily in children, in a range of 9 to 13 mg/kg (4 to 6 mg/lb) usually produce surgical anesthesia within three to four minutes following injection, with the anesthetic effect usually lasting 12 to 25 minutes.

Induction:

Intravenous Route: The initial dose of Ketalar administered intravenously may range from 1 mg/kg to 4.5 mg/kg (0.5 to 2 mg/lb). The average amount required to produce five to ten minutes of surgical anesthesia has been 2 mg/kg (1 mg/lb).

NOTE: The 100 mg/ml concentration (S-V 1585) of Ketalar, *should not* be injected intravenously without proper dilution. It is recommended the drug be diluted with an equal volume of either Sterile Water for Injection, USP, Normal Saline, or 5% Dextrose in Water.

Rate of Administration: It is recommended that Ketalar be administered slowly (over a period of 60 seconds). More rapid administration may result in respiratory depression and enhanced pressor response.

Intramuscular Route: The initial dose of Ketalar administered intramuscularly may range from 6.5 to 13 mg/kg (3 to 6 mg/lb). A dose of 10 mg/kg (5 mg/lb) will usually produce 12 to 25 minutes of surgical anesthesia.

Maintenance of Anesthesia:

Increments of one half to the full induction dose may be repeated as needed for maintenance of anesthesia. However, it should be noted that purposeless and tonic-clonic movements of extremities may occur during the course of anesthesia. These movements do not imply a light plane and are not indicative of the need for additional doses of the anesthetic.

It should be recognized that the larger the total dose of Ketalar (ketamine HCl injection) administered, the longer will be the time to complete recovery.

Supplementary Agents:

Ketalar is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained.

HOW SUPPLIED

Ketalar is supplied as the hydrochloride in concentrations equivalent to ketamine base.

N 0071-4581-15—Each 50-ml vial contains 10 mg/ml. Supplied in cartons of 10.

N 0071-4581-12—Each 20-ml vial contains 10 mg/ml. Supplied in cartons of 10.

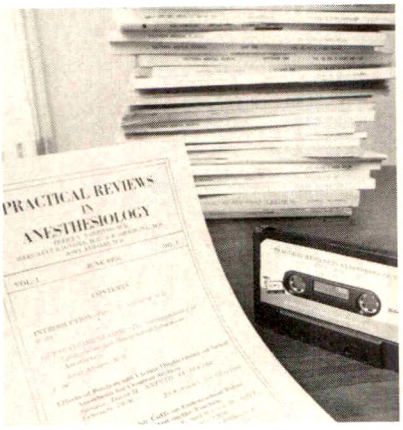
N 0071-4582-10—Each 10-ml vial contains 50 mg/ml. Supplied in cartons of 10.

N 0071-4585-08—Each 5-ml vial contains 100 mg/ml. Supplied in cartons of 10.

PD-JA-1839-1-P (4-76) SG

PARKE-DAVIS

PARKE, DAVIS & COMPANY
Detroit, Michigan 48232

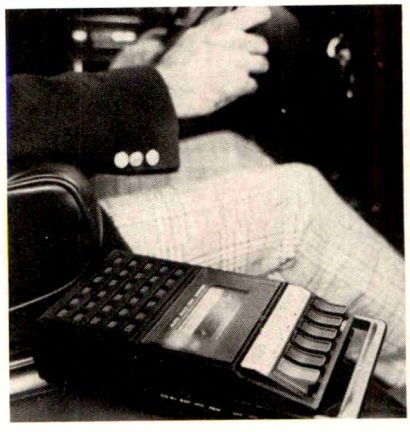


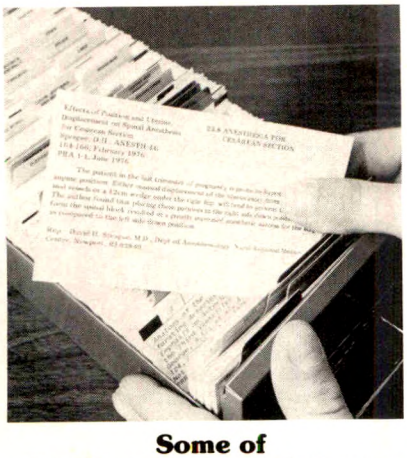
The Anesthesiologist: *You need to know it all... and now!*

Anesthesia cuts across the entire medical spectrum. And the very latest information is in the journals. But when can you find the time to read them? And even more important, to have the information at hand when you need it.

Practical Reviews can help!

Each month a group of outstanding anesthesiologists (plus distinguished guest commentators) picks the best of current information from the journals, boils it down to 3-4 minute segments and sends it to you on cassette tapes. Thus each month you get 20-25 digests of the newest and best in Anesthesiology. You can listen in any free time available, even in your car!





Information in seconds!

Best of all, each article is summarized on subject-indexed reference cards. Practical Reviews unique tab-filing system (also provided) makes instant retrieval possible. You build a library of vital information that is constantly being up-dated...automatically!

"This continuing medical education activity meets the criteria for hour-for-hour credit in Category I for the Physician's Recognition Award of the AMA."

Some of The Guest Commentators on The Practical Reviews Anesthesiology Team:

John Steinhaus, M.D.
Chairman, Department of Anesthesiology, Emory University

M. T. Jenkins, M.D.
Chief of Anesthesia, Parkland Memorial Hospital

Joachim Gravenstein, M.D.
Chairman of Anesthesiology, Case-Western Reserve School of Medicine

Robert M. Smith, M.D.
Director of Anesthesiology Children's Hospital of Boston

Joseph R. Artusio, Jr., M.D.
Chairman, Anesthesia, Cornell School of Medicine Anesthetist-in-Chief, New York Hospital

Coordinated by: Perry P. Volpitto, M.D.
Medical College of Georgia

Start your subscription now!

To: **EDUCATIONAL REVIEWS, INC.**
Box 582, Leeds, Al. 35094

Gentlemen:
Please start my subscription, including monthly cassette tapes, cross-reference summary cards, related printed material, color-tabbed index system and handsome vinyl tape-album to **PRACTICAL REVIEWS IN ANESTHESIOLOGY.**

NAME_____ SPECIALTY_____

ADDRESS_____

CITY, STATE, ZIP_____

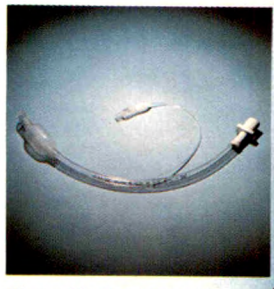
☐ Enclosed is my check for $110 for a 12 month subscription.

☐ Send me more information.

Alabama residents please add tax. Foreign subscribers add 10%

The anesthesia system without compromises is the one you design for yourself. Including Ohio keepables and disposables!

VORTEX™ Respiration Monitor measures tidal volumes continuously, totalizes to obtain minute volume.



Disposable Endotracheal Tubes, new, uncuffed or with anatomically designed cuffs for gentle seal. Unique inflation and pilot balloon assembly.

Disposable Anesthesia Breathing Circuit with conductive, cushioned masks in three sizes. Our bacteria filter-pathogen trap fits most anesthesia circuits.

OHIO Critical Care Ventilator with intermittent mandatory ventilation "engineered in." Assists ventilation in any interval from 5 to 100 seconds.

Anesthesia Ventilator, fluidically controlled for less maintenance. Precise and reliable. With a built-in gas evacuator. Ohio can also customize a gas evacuation interface to accommodate your disposal system.

O_2 Monitor with visual and audio alarms.

One system designed to suit all can't really satisfy everyone. Because somewhere along the line you have to compromise. Each of you has your own ideas about how best to provide excellence in patient care in your own operating theater. And each OR has its unique needs.

Most new systems begin with one of the four OHIO® anesthesia machines. Rugged. Practical. Versatile. Functional. Delivering your preference in anesthetic agents with accuracy and safety.

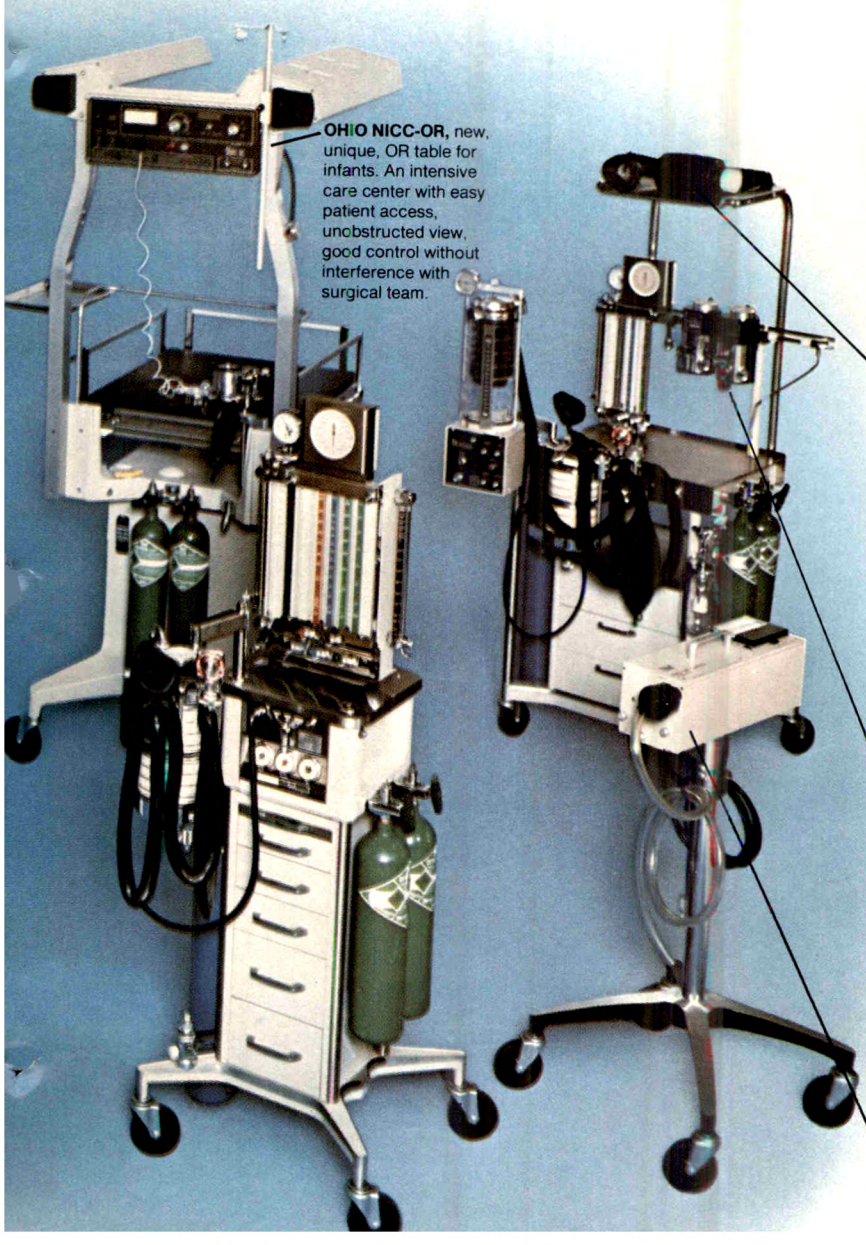
Then, your system grows to support your skills and techniques, as you add accessories and options from Ohio: Vaporizers, ventilators and absorbers, monitors, disposables, medical gases, and gas evacuation systems. And we always have more on the way.

You can depend on over 100 factory-trained Ohio servicemen and six service centers in the U.S. and Canada to keep your anesthesia equipment performing. Plus a knowledgeable sales staff.

Send for information. Or send for your salesman. Ohio will help you develop a reliable, sophisticated anesthesia system. One you can build on when future technologies develop. So, you'll never have to compromise in caring for your patients.

Ohio Medical Products AIRCO®

3030 Airco Drive, P.O. Box 7550, Dept. 305
Madison, Wisconsin 53707



OHIO NICC-OR, new, unique, OR table for infants. An intensive care center with easy patient access, unobstructed view, good control without interference with surgical team.

HOPE® II resuscitator with a new valve and the facility to administer enriched oxygen concentrations.

OHIO Calibrated Vaporizer, new, easy-to-use, temperature and flow compensated with excellent low-flow performance.

New Trace Gas Analyzer detects and measures the concentration of nitrous oxide in the operating room atmosphere; alerting OR personnel to leak sources.

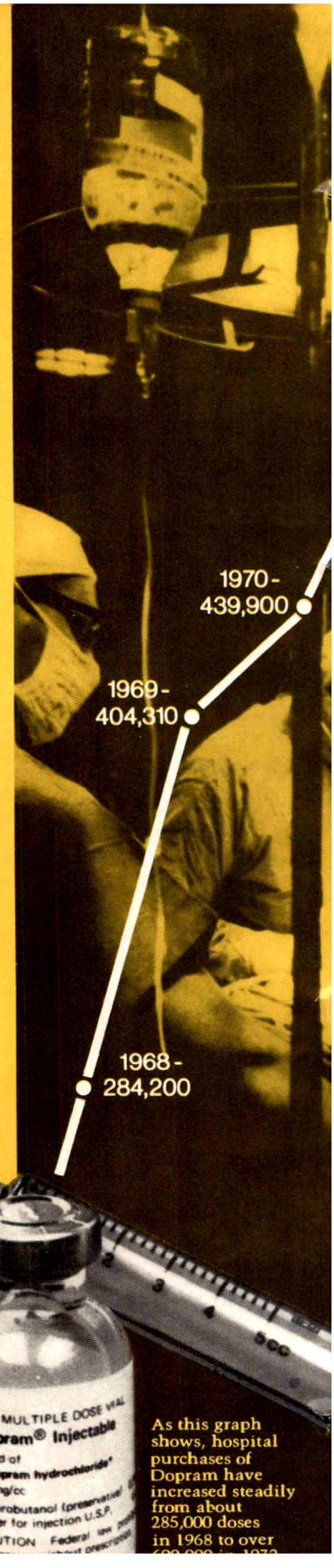
In all types of hospitals across the United States, its usage grows–

Dopram®
Injectable
(doxapram HCl)

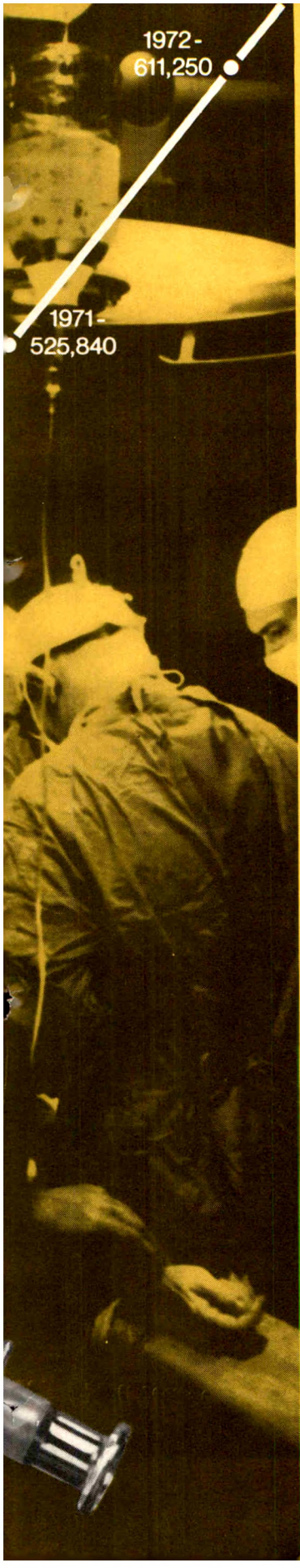
Seven years ago, A. H. Robins introduced Dopram, a unique respiratory stimulant developed in the company's research laboratories. What made this drug so useful to the anesthesiologist was its ability to rapidly restore the respiratory drive in patients with drug-induced post anesthetic depression.

Usage of Dopram has been steadily increasing each year, until today it has become a very important drug in the armamentarium of more than 1,500 hospitals of all types in all 50 states, the District of Columbia, and a number of foreign countries. These hospitals purchased more than 600,000 doses in 1972 alone.

Dopram–an important drug in anesthesiology. Try it for sighs!



As this graph shows, hospital purchases of Dopram have increased steadily from about 285,000 doses in 1968 to over



Indications

1. To stimulate respiration in patients with drug induced post-anesthetic respiratory depression or apnea other than that due to muscle relaxant drugs.
2. To pharmacologically stimulate deep breathing in the so-called "stir-up" regimen in the post-operative patient. Simultaneous administration of oxygen is desirable.
3. To hasten arousal and return of protective pharyngeal and laryngeal reflexes.
4. To aid in the differential diagnosis of post-anesthetic respiratory depression. Failure to adequately stimulate respiration suggests residual muscle relaxant effect.
5. To stimulate respiration, hasten arousal and to encourage the return of laryngopharyngeal reflexes in patients with mild to moderate respiratory and CNS depression due to drug overdosage.

Contraindications—Epilepsy and other convulsive states: incompetence of the ventilatory mechanism due to muscle paresis, flail chest, pneumothorax, airway obstruction, and extreme dyspnea; severe hypertension and cerebrovascular accidents; hypersensitivity.

Doxapram is not recommended for patients 12 years of age or under because studies to evaluate its safety and efficacy have not been performed.

Warnings—Doxapram is an analeptic agent; it is neither an antagonist to muscle relaxant drugs nor a specific narcotic antagonist. Since doxapram has an acid pH, it should not be mixed with alkaline solutions such as thiopental sodium.

Since narcosis may recur after stimulation with doxapram, care should be taken to maintain close observation until the patient has been fully alert for 1/2 to 1 hour. (Duration of drug 5-12 minutes.)

Doxapram is an adjunct to well-accepted supportive measures and resuscitative techniques. It may not stimulate adequate spontaneous breathing or provide sufficient arousal in patients who are severely depressed with CNS depressant drugs.

When doxapram is administered to postoperative patients or to patients in a state of narcosis with chronic pulmonary insufficiency, oxygen should be administered concomitantly. Failure to do so may result in further oxygen debt and more severe dyspnea due to the increased work of breathing.

Doxapram should be administered with great care and only under close supervision to patients with cerebral edema, bronchial asthma, severe tachycardia, cardiac arrhythmia, cardiac disease, hyperthyroidism and pheochromocytoma.

Usage in pregnancy

No adequate clinical studies have been performed to determine the safe use of doxapram in pregnancy. Until further clinical experience has been obtained, the physician must weigh the need against possible risks in using the drug in pregnant patients or in women of child-bearing potential.

Precautions—Recommended dosages of doxapram should be employed and maximum total dosages should not be exceeded. In patients with advanced pulmonary disease with hypoxemia, marked respiratory stimulation increases the work of breathing and may, thus, increase oxygen consumption and carbon dioxide production.

With excessive dosage, hyperventilation induced by doxapram may lead to respiratory alkalosis and hypocapnia with tetany and, theoretically, apnea.

An adequate airway is essential. In order to avoid side effects, it is advisable to use the minimum effective dosage. Monitoring of the blood pressure and deep tendon reflexes is recommended to prevent overdosage.

It is desirable that blood gases (P_{O_2} P_{CO_2} O_2 saturation) be monitored to assess the effectiveness of respiratory stimulation.

Intravenous barbiturates, oxygen and resuscitative equipment should be readily available to manage overdosage manifested by excessive central nervous system stimulation. Slow administration of the drug and careful observation of the patient during administration and for some time subsequently are advisable to insure restoration of the protective reflexes. The possibility of post-stimulation respiratory depression must be kept in mind. In patients who have been lightly curarized, doxapram may temporarily mask the residual effects of muscle relaxant drugs.

Doxapram should be administered cautiously to patients receiving sympathomimetic or monoamine oxidase inhibiting drugs, since a synergistic pressor effect may occur. It should likewise be used with care in post-operative patients with marked dyspnea due to obstructive pulmonary emphysema, acute or chronic asthma, profound metabolic disorders, severe to moderately severe hypertension, increased cerebrospinal fluid pressure, head injury and acute agitation.

Since doxapram may stimulate basal gastric secretion, it should be used with care in patients with peptic ulcer disease and in patients undergoing gastric surgery.

Vascular extravasation or use of a single injection site over an extended period should be avoided since either may lead to thrombophlebitis.

Hypocapnia accompanying forced ventilation is a potent stimulus to cerebral vasoconstriction; it may be postulated that some element of risk may exist from reduced cerebral blood flow following prolonged and intensive hyperventilation.

Since an increase in epinephrine release has been noted with doxapram, it is recommended that initiation of therapy with this respiratory stimulant be delayed for at least 10 minutes following the discontinuance of anesthetics known to sensitize the myocardium to catecholamines, such as halothane and cyclopropane.

As with other intravenous preparations, all precautions should be taken during administration of doxapram to insure that injection is made directly into a suitable vein; extravasation, and inadvertent intra-arterial injection should be avoided.

Adverse reactions—The following adverse reactions have been reported: *Central and Autonomic Nervous Systems.* Hyperactivity, feeling of warmth, sweating, muscle tremor, clonus, increased deep tendon reflexes, dizziness, muscle spasticity, pyrexia, confusion, paresthesia, pupillary dilatation, pilomotor erection, headache, bilateral babinski, fasciculation and carpopedal spasm. A grand mal seizure occurred 95 minutes after drug administration in a known epileptic patient who was on anticonvulsant medication.

Respiratory. Cough, dyspnea, laryngospasm, bronchospasm and hiccough.

Cardiovascular. Hypertension, sinus tachycardia, bradycardia, extrasystoles, lower T-waves, premature ventricular contractions, irregular heart rhythm, tightness in chest. Although a mild to moderate increase in blood pressure is not infrequent, such an increase may occasionally be of concern in hypertensive patients.

Gastrointestinal. Nausea and/or vomiting, salivation, stimulation of lower bowel, sour taste.

Genitourinary. Urinary retention, stimulation of urinary bladder with spontaneous voiding.

Miscellaneous. Pruritus, thrombophlebitis.

Laboratory Determinations. A decrease in hemoglobin, hematocrit, or red blood cell count has been observed in postoperative patients. In the presence of pre-existing leukopenia, a further decrease in WBC was observed following anesthesia and treatment with doxapram hydrochloride. Elevation of BUN and albuminuria have been observed.

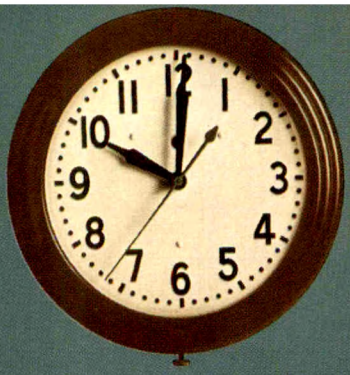
In some of the cases cited above, the patients had received multiple drugs concomitantly, thus preventing an absolute judgment as to the role of doxapram in these reactions.

Dosage—For complete information concerning dosage and administration see package insert.

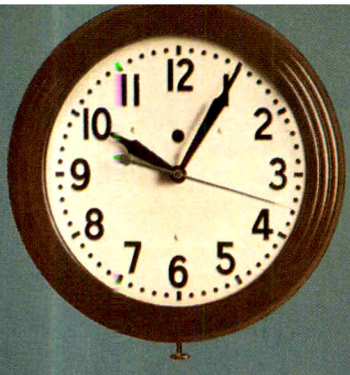
Supply—Dopram (doxapram hydrochloride) is available in 20 cc rubber stoppered vials containing 20 mg/cc, with chlorobutanol 0.5% as the preservative.

A. H. Robins Company
Richmond, Virginia 23220

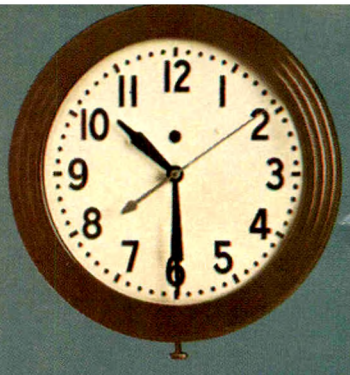
A·H·ROBINS



SUBLIMAZE® (fentanyl) has a uniquely short duration of analgesic action—for more precise control and minimal risk of prolonged narcotic effects.

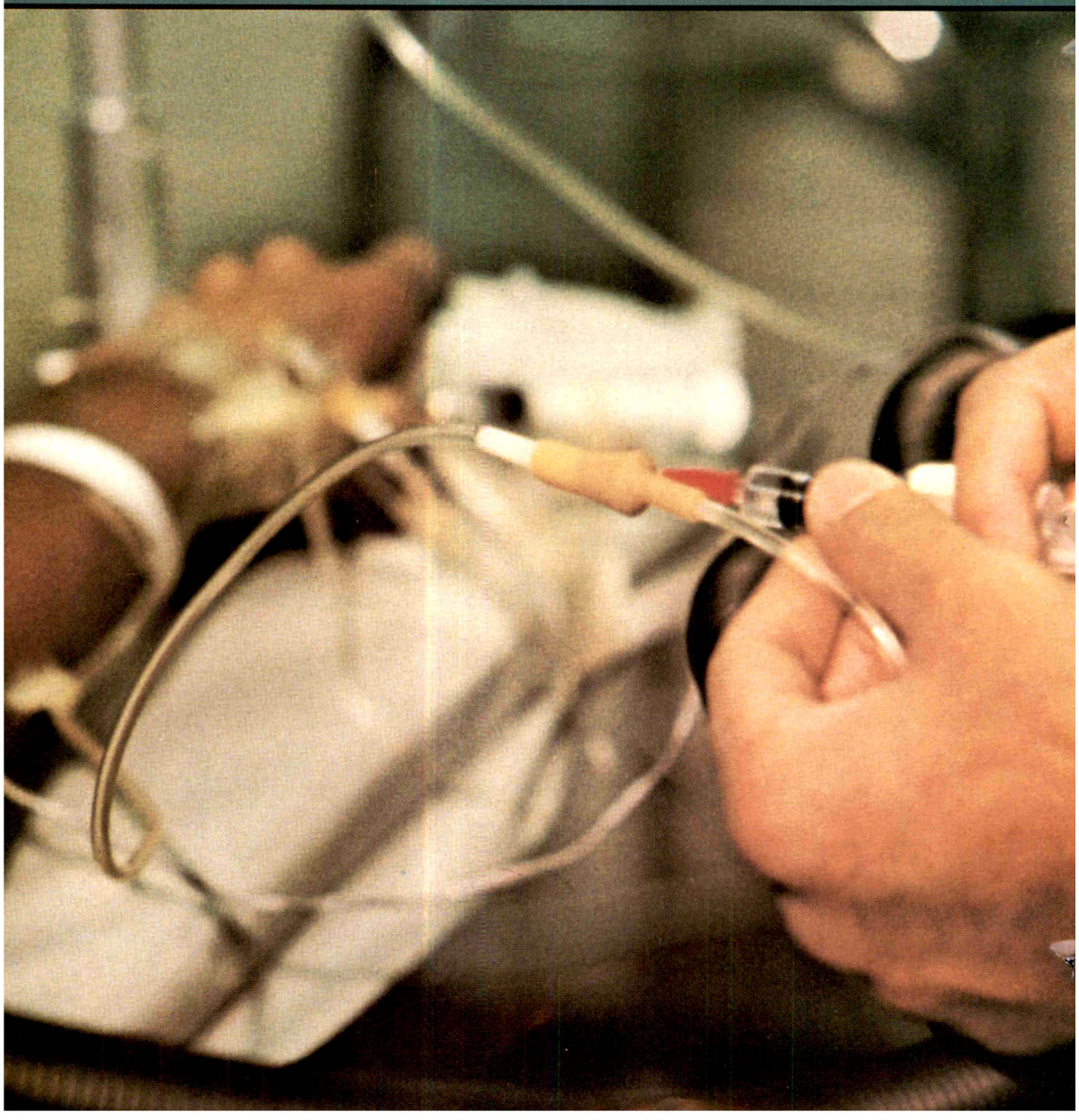


Within 5 minutes I.V., SUBLIMAZE® (fentanyl) reaches its peak analgesic effect.



Within 30 to 60 minutes I.V., the analgesic effect of SUBLIMAZE® (fentanyl) is almost completely dissipated.†

† Respiratory depressant effects may last longer than the analgesia and are increased and prolonged with larger doses, multiple doses or use of postoperative narcotic analgesics.



For potent narcotic analgesic action with rapid onset and short duration:

SUBLIMAZE fentanyl provides profound analgesia without hypnosis and with little or no sedation. With this analgesia as a foundation, it is possible to use light general anesthesia in most cases.

SUBLIMAZE fentanyl is particularly suited for maintenance of analgesia after INNOVAR® injection* has been used for induction. It may also be used preoperatively, during surgery with any common general or regional anesthetic agent, and in the immediate postoperative period whenever the need for potent analgesic action arises.

SUBLIMAZE fentanyl is available both alone and as a component of INNOVAR injection.*

*INNOVAR injection is composed of a 50:1 mixture of droperidol 2.5 mg./cc. and fentanyl 0.05 mg./cc., with lactic acid for adjustment of pH to 3.5 ± 0.3.

SUBLIMAZE® (fentanyl) offers:

☐ Almost immediate analgesia—peak effect within 5 minutes I.V., 8 minutes I.M.

☐ Short duration of analgesic action—30 to 60 minutes with a single I.V. dose of up to 0.1 mg. (Respiratory depressant effects may last longer than the analgesia and are increased and prolonged with larger doses, multiple doses or use of postoperative narcotic analgesics.)

☐ No evidence of liver, heart, or kidney toxicity—expecially valuable in poor-risk patients. However, the drug should be administered cautiously in the presence of liver or kidney dysfunction or cardiac arrhythmias, and the dose should be appropriately reduced in poor-risk patients.

☐ Immediate reversibility by narcotic antagonists.

☐ Little or no histamine release—decreasing the risk of cardiovascular instability.

☐ Minimal emetic effect—has been used successfully to prepare nonfasting patients for awake intubation.

☐ Prevention or reversal of emergence delirium and tachypnea.

SUBLIMAZE® (fentanyl) injection

0.05 mg./cc. as the citrate.
Warning: May be habit forming.
Sodium hydroxide for adjustment of pH to 4.0—7.5

INNOVAR® injection and SUBLIMAZE® (fentanyl) injection are available for use only upon direction of a physician.
For information relating to Contraindications, Warnings, Precautions and Adverse Reactions for SUBLIMAZE fentanyl, please turn page.

© McNeil Laboratories, Inc., 1974

SUBLIMAZE® (fentanyl) injection

Description
Each cc. contains:
Fentanyl as the citrate ..... 0.05 mg.
Warning—May be habit forming.
Sodium hydroxide for adjustment of pH to 4.0–7.5
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY.

Actions SUBLIMAZE fentanyl is a narcotic analgesic with actions qualitatively similar to those of morphine and meperidine. SUBLIMAZE fentanyl in a dose of 0.1 mg. (2.0 cc.) is approximately equivalent in analgesic activity to 10 mg. of morphine or 75 mg. of meperidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. SUBLIMAZE fentanyl appears to have less emetic activity than other narcotic analgesics. Histamine assays and skin wheal testing in man, as well as *in vivo* testing in dogs, indicate that histamine release rarely occurs with SUBLIMAZE fentanyl.

SUBLIMAZE fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. It may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia, and bronchoconstriction.

The onset of action of SUBLIMAZE fentanyl is almost immediate when the drug is given intravenously; however, maximal analgesic and respiratory depressant effect may not be noted for several minutes. The average duration of action of the analgesic effect is 30 to 60 minutes. Following intramuscular administration, the onset of action is from seven to eight minutes, and the duration of action is from one to two hours.

Although the duration of the respiratory depressant effect is unknown, as with other narcotic analgesics it may be considerably longer than the analgesic effect.

Indications SUBLIMAZE fentanyl is indicated:
—for analgesic action of short duration during the anesthetic periods, premedication, induction, and maintenance, and in the immediate postoperative period (recovery room) as the need arises.
—for use as a narcotic analgesic supplement in general or regional anesthesia.
—for administration with a neuroleptic such as INAPSINE® (droperidol) injection as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.

Contraindications SUBLIMAZE fentanyl is contraindicated in patients who are hypersensitive to the drug.

Warnings PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* FENTANYL SHOULD HAVE APPROPRIATE SURVEILLANCE.

RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

If SUBLIMAZE fentanyl is administered with a tranquilizer such as INAPSINE droperidol, the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE fentanyl persists longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as 1/4 to 1/3 those usually recommended. A neuromuscular blocking agent compatible with the patient's condition may be required to control muscle rigidity which may develop with the use of SUBLIMAZE fentanyl.

Drug Dependence: SUBLIMAZE fentanyl can produce drug dependence of the morphine type and therefore has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE fentanyl in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure: SUBLIMAZE fentanyl should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition, SUBLIMAZE fentanyl may obscure the clinical course of patients with head injury.

Usage in Children: The safety of SUBLIMAZE fentanyl in children younger than two years of age has not been established.

Usage in Pregnancy: The safe use of SUBLIMAZE fentanyl has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

Precautions *The initial dose of SUBLIMAZE fentanyl should be appropriately reduced in elderly, debilitated and other poor risk patients. The effect of the initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms (see Actions) SUBLIMAZE fentanyl can also alter respiration. When SUBLIMAZE fentanyl is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia. When used with a tranquilizer such as INAPSINE droperidol, blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE fentanyl should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Postoperatively, respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists (levallorphan, nalorphine, and naloxone; consult individual prescribing information before using). Should respiration be compromised by muscle rigidity, assisted or controlled respiration and possibly a neuromuscular blocking agent will be required. The occurrence of muscle rigidity is related to the speed of intravenous injection and the incidence can be reduced by slow intravenous injection.

When a tranquilizer such as INAPSINE droperidol is used with SUBLIMAZE fentanyl, pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE fentanyl. When patients have received such drugs, the dose of SUBLIMAZE fentanyl required will be less than usual. Likewise, following administration of SUBLIMAZE fentanyl the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE fentanyl should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE fentanyl may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE fentanyl should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE fentanyl is used with a tranquilizer such as INAPSINE droperidol, hypotension can occur. If this occurs the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of INAPSINE droperidol, epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE droperidol.

Adverse Reactions As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE fentanyl are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur.

Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

When a tranquilizer such as INAPSINE droperidol is used with SUBLIMAZE fentanyl, the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with antiparkinson agents. Postoperative drowsiness is also frequently reported following the use of INAPSINE droperidol.

Overdosage ***Manifestations:*** The manifestations of SUBLIMAZE fentanyl overdosage are an extension of its pharmacologic actions.
Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan, or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. Consult the package insert for the individual narcotic antagonists for details about use.

How Supplied SUBLIMAZE® (fentanyl) injection is supplied in 2 cc. (**NDC** 0045-0180-03) and 5 cc. (**NDC** 0045-0180-05) ampuls, in packages of 12.

IMPORTANT: Complete dosage information is available in insert which accompanies each package (or on request). The drug is available only upon direction of a physician.

U.S. Patent No. 3,164,600 9/74

McNEIL McNeil Laboratories, Inc.
Fort Washington, Pa. 19034

PEOPLE and PLACES

Carter M. Ballinger, MD, has been appointed chairman of the Department of Anaesthesiology at the New Jersey Medical School of the College of Medicine and Dentistry of New Jersey. Dr. Ballinger was formerly associated with the University of Utah, holding the rank of associate professor and chairman of anesthesiology.

★ ★ ★

The Department of Anesthesiology, Naval Regional Medical Center, Portsmouth, Virginia, in cooperation with the Virginia Society of Anesthesiologists, is sponsoring the Seventh Annual Anesthesiology Symposium September 9-11, 1976. This will be a refresher course directed towards the continuing education of anesthesiologists and anesthetists. The symposium will be held in the Holiday Inn Scope, Norfolk, Virginia.

★ ★ ★

The autumn meeting of the Obstetric Anaesthetists Association will be held Friday, September 24, 1976, at the Withington Hospital, University of South Manchester. Hostess: **Dr. Valerie Hey.**

The 1977 spring meeting will be held Friday, April 22, 1977, at the University of Newcastle. Hosts: **Drs. J. Storrs** and and **M. Bryson.** Papers for this meeting should be sent not later than January 1, 1977, to **Dr. B. A. Waldron,** City Hospital, Hucknall Road, Nottingham, NGS 1PB.

Regional Anesthesia, sponsored by the Anesthesiology Educational Foundation will be held October 15, 16 and 17, 1976, at the Holiday Inn, Monterey, California. For further information, write to: **Ronald L. Katz, MD,** Department of Anesthesiology, UCLA Center for Health Sciences, Los Angeles, California 90024.

★ ★ ★

Anesthesia and Surgery of Ischemic Heart Disease will be presented by the Department of Anesthesiology and the Office of Continuing Education, Baylor College of Medicine, November 17, 18 and 19, 1976, at the Shamrock Hilton Hotel, Houston, Texas. This Continuing Medical Education offering meets the criteria for 12 hours of credit in Category 1 for the Physician's Recognition Award of the American Medical Association.

★ ★ ★

The Czechoslovak Society of Anaesthesiology and Resuscitation, commissioned by the Czechoslovak Medical Society, **J. E. Prukyně,** will hold their second Congress of Anaesthesiologists and eighth International Symposium May 25-27, 1977, in Bratislava. For more information write to: **J. Malatinský, MD,** Secretary General of the Congress, Congress Office, Slovak Medical Society, Mickiewiczova 18, 883 22 Bratislava, CCSR.

★ ★ ★

The Second Malaysian Congress of Anaesthesiologists will be held in Kuala Lumpur, Malaysia, at the General Hospital, October 21-23, 1977. This congress is organized by the Malaysian Society of Anaesthesiologists. Further information can be obtained from: Hon. Organizing Secretary, Second Malaysian Congress of Anaesthesiologists, P.O. Box S-20, Sentul, 124 Jalan Pahang, Kuala Lumpur 02-14, Malaysia.

★ ★ ★

The Johns Hopkins Medical Institutions is sponsoring a two-day symposium on "Critical Care Monitoring," October 22-23, 1976. This symposium is designed to cover all facets of advanced management of the critically ill patient. Basic program components will include the continuous EEG, management of arrhythmias, basic instrumentation; advanced invasive hemodynamic monitoring, cardiac output, and the management of patients with specific problems.

The course is approved for 16 credit hours (Category I) towards the Physician's Recognition Award of the American Medical Association.

For further information contact: **Janet B. Hardy, M.D.,** Office of Continuing Education, Room 17, Turner Auditorium, Baltimore, Maryland 21205.

Anaesthesia Annual Fall Scientific Meeting Section on Anaesthesia, Ontario Medical Association, Ontario Division, Canadian Anaesthetists' Society Meeting will be held in London, Ontario, at the Holiday Inn City Centre, September 23-25, 1976. Meeting Coordinator is **Dr. G. R. Sellery**, Victoria Hospital, London, Ontario, Canada.

★ ★ ★

Dr. Leonard C. Jenkins, Vancouver, British Columbia, Canada; **Dr. John J. Savarese**, Boston, Massachusetts; and **Dr. N. Ty Smith**, San Diego, California, have been appointed Contributing Editors of *Anesthesia and Analgesia . . . Current Researches.*

★ ★ ★

The First Annual Caribbean Symposium in Anesthesiology and Related Fields will be held in San Juan, Puerto Rico, from December 12-15, 1976. Held under the auspices of the Department of Anesthesiology, Teacher's Hospital, San Juan, and the Puerto Rican Society of Anesthesiologists, the first Symposium will be devoted to the topic of Pulmonary Aspiration and the First Caribbean Lecture in Anesthesiology will be given by Professor Jerome H. Modell on "Near Drowning."

For further information contact: **Miguel Colón-Morales, M.D.**, G.P.O. Box 4547, San Juan, Puerto Rico 00936.

★ ★ ★

An opportunity for anesthesiologists and obstetricians/gynecologists to learn or review principles and practices of anesthesia and analgesia for obstetrics and gynecology is being offered in the Department of Anesthesiology at the Valley Medical Center in Fresno, California, under the direction of **John S. McDonald, M.D.**, Chairman of the Department. Four and eight week rotations would include general and regional anesthesia and didactic training in the pharmacology of drugs.

Applicants should be trained in the United States and must possess State or National Board Licensure. In some instances, foreign graduates who have passed the FLEX examination or the equivalent thereof will be considered. More infor-fation may be obtained by writing to **John S. McDonald, M.D.**, P.O. Box 7632, Fresno, California 93727, (209) 251-4833, ext. 2228.

In 16 years of use in the United States, FLUOTHANE (halothane) has been administered over 100 million times in a wide variety of surgical procedures. 100 million . . . extensive usage and evaluation that attests to FLUOTHANE as the most widely used inhalant anesthetic.

Since it was first introduced, over 4,000 papers worldwide have been published, ranging from review articles to in-depth studies. 4,000 papers . . . a bibliographic record of note on the most widely used inhalant anesthetic.

In a continuing program of informational services on anesthesiology, Ayerst provides printed and audiovisual aids reflecting the opinions and experiences of recognized authorities in the field. These include the highly regarded series on *Anesthesia Rounds* and *Clinical Aspects of Anesthesiology*, as well as several films of educational value—all available through your Ayerst Representative.

FLUOTHANE® (HALOTHANE) ...OVER 100 MILLION ADMINISTRATIONS

- nonflammable, nonexplosive
- permits use of high concentrations of oxygen
- allows free use of cautery for more adequate control of bleeding
- minimal odor facilitates smooth, rapid induction, reduces patient distress
- early obtundation of pharyngeal and laryngeal reflexes facilitates intubation
- lessens airway problems
- permits rapid adjustment of depth of anesthesia
- emergence is rapid and tranquil with quick recovery of protective reflexes
- minimal nausea and vomiting, shorter recovery room stay

Ayerst®

See last page of advertisement for prescribing information.

FLUOTHANE®

brand of halothane

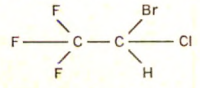
the most widely used inhalant anesthetic

from Ayerst

for precision, experience, quality, and service

(Complete text of package circular.)

Description. FLUOTHANE, brand of halothane, is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20° C., and the boiling point (range) is 49° C.-51° C. at 760 mm. Hg. The vapor pressure is 243 mm. Hg at 20° C. The blood/gas coefficient is 2.5 at 37° C., and the olive oil/water coefficient is 220 at 37° C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. FLUOTHANE is soluble in rubber, some plastics, and similar materials; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizing bottles not specifically designed for its use. It is recommended that vaporizers be emptied at the end of each operating day. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE should be avoided when a previous exposure was followed by fever and jaundice, or when there was an unexplained postoperative fever.

FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy: Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

Adverse Reactions. The following adverse reactions have been reported: hepatic necrosis, cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide (usually in a 50:50 ratio).

How Supplied. No. 3125—Unit packages of 125 cc. and 250 cc. of halothane stabilized with 0.01% thymol (w/w).

7522

Ayerst **AYERST LABORATORIES**
New York, N.Y. 10017

When you need to know

DINAMAP for **non-invasive,** routine monitoring of arterial pressure.‡

Using: An ordinary pressure cuff with no transducer. Easily attached to any limb.*

Provides: Automatic determination and digital display of mean arterial pressure.

Write or call for your demonstration.

Applied Medical Research
6 Columbia Drive
Tampa, Fla. 33606
(813) 251-8390 Dept. 3

‡Audible pulse monitor optional.
*Including patient preferred ankl

THE MOST POPULAR MONITORS MADE. MADE EVEN BETTER.

For some time now, our monitors have been selected for use in surgery by more medical people than any other battery-powered monitors in the world. Because we give you more of what you want in a monitor than any other monitors in the world.

However, this didn't stop us from improving them.

Our new Datascope 851 and 861 will now give you heart rate not only from ECG, but also from pulse or blood pressure.

And both monitors will give you 2 traces. So you can monitor ECG (or EEG) and pulse simultaneously.

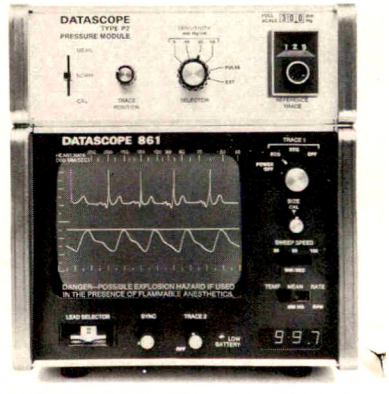
And both give you beat by beat synchronization†. So a single ECG complex shows up with each full sweep.

The 861 does even more. It monitors body temperature. On a digital read-out. And this same digital display will give you heart rate when you want it; or mean blood pressure when you are using the 861 with our Pressure Module.

For all the things our 851 and 861 do, they're surprisingly portable. And they offer longer battery-operating time than any other monitors. In some cases, actually twice as long.

Will they continue to be the most popular monitors made? More so.

For further information about our new 851, 861, or our Pressure Module, write Datascope Corp., 580 Winters Ave., Paramus, NJ 07652.

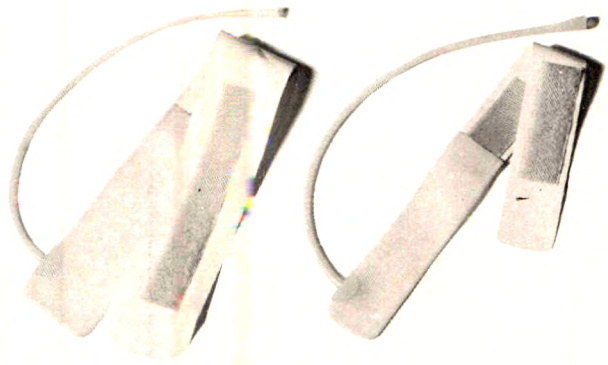


The 861 with Pressure Module.

THE DATASCOPE 851/861

†U.S. PATENT NO. 3457452

The tender touch

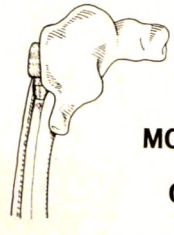


These soft, pliable blood pressure cuffs are ideal for use on newborns and infants. Incorporating a Latex bladder, minimizing any chances for skin irritation, and Silicon wrap-around with 12-inch inflating tube. They are secured by the Velcro hook and pile method, with no eyes to hook nor ends to tuck in. They are instantly peeled apart for easy removal.

Cuffs are available in two sizes:
22080 - 1⅜ x 5" (new born)
22081 - 2¼ x 6" (infant)

For additional information write for brochure number 27.

DUPACO
INCORPORATED
P.O. Box 98,
San Marcos, CA 92069



FOR MONOSCOPE MONITORING COMFORT CUSTOM EARPIECE

Made From Your Own Ear Impression

"Do It Yourself Impression Procedure" Proven At Many Hospitals Over Period of Several Years.

Impression Kit and Full Instructions Complete With Postage Prepaid Mailer $1.00

Lucite Custom Earmold With Coupler . . $8.50

One Week Delivery. Full Guarantee.
Full information upon request.

PLASTICAST LABORATORIES, INC.

711 Penn Ave. Pittsburgh, Pa. 15222

I.A.R.S. EDUCATIONAL MEMBERSHIP FOR ALL STUDENTS IN ANESTHESIA TRAINING PROGRAMS

Two-year, one-half price membership, including subscription to ANESTHESIA and ANALGESIA . . . Current Researches.

Application forms available from Cleveland business office. Certification by Program Director required.

Nesacaine®
(Chloroprocaine Hydrochloride)

1% and 2% solution in 30-ml. multiple-dose vials

For Infiltration and Regional Anesthesia

Nesacaine®-CE
(Chloroprocaine Hydrochloride)

2% and 3% solution in 30-ml. single-dose vials

For Caudal and Epidural Anesthesia

INDICATIONS

NESACAINE in multiple dose vials and NESACAINE-CE in single dose vials without preservatives are indicated for production of local anesthesia by infiltration injection and nerve block.*

*NESACAINE in multiple dose vials with preservatives is not to be used for caudal or epidural anesthesia. NESACAINE-CE contains no preservatives and the unused portion must be discarded after initial use.

CONTRAINDICATIONS

NESACAINE and NESACAINE-CE are contraindicated in patients hypersensitive to drugs of the PABA ester group. Central nervous system disease is generally considered a contraindication to caudal or epidural nerve block.

WARNINGS

RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE IMMEDIATELY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED. As NESACAINE-CE contains no preservative, discard unused drug remaining in vial after initial use. Equipment and drugs necessary for the treatment of inadvertent intravascular injection, intrathecal injection, or excessive dosage should be immediately available.

Usage in Pregnancy: Safe use of chloroprocaine hydrochloride has not been established with respect to adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential unless in the judgment of the physician the potential benefits outweigh the unknown hazards. In obstetrics, if vasoconstrictor drugs are used either to correct hypotension or are added to the local anesthetic solution, the obstetrician should be warned that some oxytocic drugs may cause severe persistent hypertension and even rupture of a cerebral blood vessel may occur during the post partum period.

Solutions containing vasoconstrictors, particularly epinephrine and norepinephrine, should be used with extreme caution in patients receiving certain antidepressants such as MAO inhibitors, and tricyclic compounds since a severe prolonged hypertension may occur.

PRECAUTIONS

The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious undesirable systemic side effects. Tolerance varies with the status of the patient. Debilitated patients, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical status.

Solutions containing vasoconstrictors should be used cautiously in the presence of disease which may adversely affect the patient's cardiovascular system.

Chloroprocaine hydrochloride should be employed cautiously in persons with known drug allergies or sensitivities.

The decision whether or not to use local anesthesia in the following conditions depends on the physician's appraisal of the advantages as opposed to the risk:

Paracervical block when fetal distress is anticipated or when predisposing factors causative of fetal distress are present (i.e., toxemia, prematurity, diabetes, etc.). Injection of solutions containing epinephrine in areas where the blood supply is limited (i.e., ears, nose, digits, etc.) or when peripheral vascular disease is present.

ADVERSE REACTIONS

Adverse reactions result from high plasma levels due to rapid absorption, inadvertent intravascular injection or excessive dosage. Hypersensitivity, idiosyncrasy, or diminished tolerance are other causes of reactions. Reactions due to overdosage (high plasma levels) are systemic and involve the central nervous system and the cardiovascular system.

Reactions involving the central nervous system are characterized by excitation and/or depression. Nervousness, dizziness, blurred vision or tremors may occur followed by drowsiness, convulsions, unconsciousness and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestations may be drowsiness merging into unconsciousness and respiratory arrest.

Reactions involving the cardiovascular system include depression of the myocardium, hypotension, bradycardia and even cardiac arrest.

Treatment of a patient with toxic manifestations consists of maintaining an airway, and supporting ventilation using oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system consists of using vasopressors, preferably those that stimulate the myocardium (e.g., ephedrine) and intravenous administration in small increments of an ultrashort acting barbiturate (i.e., thiopental, thiamylal) or a short acting barbiturate if these are not available (secobarbital, pentobarbital) or a short acting muscle relaxant (succinylcholine), together with oxygen. Muscle relaxants and intravenous barbiturates should be used only by those familiar with their use.

Allergic reactions are characterized by cutaneous lesions, urticaria, edema and other manifestations of allergy. The detection of sensitivity by skin testing is of doubtful value.

DOSAGE AND ADMINISTRATION

The maximum single recommended doses of chloroprocaine hydrochloride are: without epinephrine, 800 mg.; with epinephrine (1:200,000), 1000 mg. The recommended dosage is based on requirements for the average adult and should be reduced for elderly or debilitated patients and children.

The recommended doses given below serve only as a guide to the amount of anesthetic required for most routine procedures.

1. INFILTRATION AND NERVE BLOCK (NESACAINE)

Type of Block	Volume	Concentration
Occipital	3-5 ml.	1%-2%
Mandibular	2-3 ml.	2%
Maxillary	2-3 ml.	2%
Infra-orbital	0.5-1 ml.	2%
Cervical	3-4 ml. (for each segment)	1%-2%
Brachial plexus	30-40 ml.	2%
Ulnar nerve	3-5 ml.	2%
Paravertebral	3-5 ml.	2%
Intercostal	3 ml.	1%-2%
Sciatic nerve	10-15 ml.	2%
Stellate ganglion	5-10 ml.	1%-2%
Lumbar sympathetic (1 needle technic)	15-20 ml.	1%-2%
Interdigital	3-4 ml. (without epinephrine)	1%-2%

Fractional doses, up to 300 to 600 mg., may be given at 50 minute intervals.

2. CAUDAL AND EPIDURAL BLOCK (NESACAINE-CE)

For *caudal anesthesia* the initial dose is 15 to 25 ml. of a 2% or 3% solution. Repeated doses may be given at 40 to 60 minute intervals.

For *epidural anesthesia* in the lumbar and sacral regions 2.0 to 2.5 ml. per segment of a 2% or 3% solution can be used. The usual total volume of Nesacaine-CE is from 15 to 25 ml. Repeated doses 2 to 6 ml. less than the original dose may be given at 40 to 50 minute intervals.

HOW SUPPLIED

Nesacaine is supplied as follows:

1% solution (10 mg/ml.) in 30 ml. multiple-dose vials, 12 vials per carton.

2% solution (20 mg/ml.) in 30 ml. multiple-dose vials, 12 vials per carton.

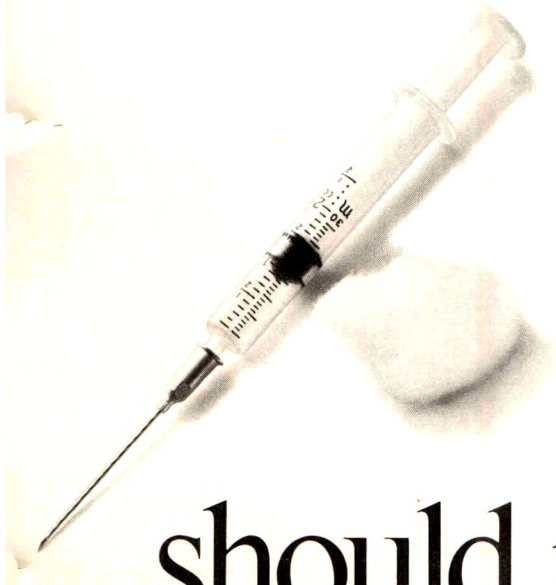
Nesacaine-CE is supplied as follows:

2% solution (20 mg/ml.) in 30 ml. single-dose vials, 12 vials per carton.

3% solution (30 mg/ml.) in 30 ml. single-dose vials, 12 vials per carton.

PENNWALT

Pennwalt Prescription Products
Pharmaceutical Division
Pennwalt Corporation
Rochester, New York 14603



A local anesthetic should meet your needs...

Rapid Onset of Action. Saves doctor, nurse and patient time.

Effective Anesthesia. Nesacaine (Chloroprocaine Hydrochloride) offers 80% to 90% pain-free procedures at recommended doses.

Exceptional Safety. Less potential for postoperative complications. Nesacaine is rapidly hydrolized in plasma, whereas lidocaine and other amide-type local anesthetics are metabolized in the liver. With Nesacaine, therefore, there is minimal potential risk of systemic toxicity, accumulation of metabolites, stimulation of CNS or cardiovascular effects.

Excellent Penetration. Chloroprocaine's lipid solubility and ionization characteristics impart it with excellent penetration.

Minimal Irritation at Injection Site. Few patient complaints about procedural pain, little soreness and inflammation after procedure.

Rapid and Complete Wear-Off. No residual numbness, patient back to normal faster.

See opposite page for brief prescribing information.

Look into

Nesacaine®

(Chloroprocaine Hydrochloride)

It meets your needs.

51ST CONGRESS

MARCH 6-10, 1977

International Anesthesia Research Society

DIPLOMAT RESORT AND COUNTRY CLUBS
HOLLYWOOD, FLORIDA

IMPORTANT INFORMATION ON THE 51st CONGRESS

Scientific Program—August 2, 1976, deadline for submission of titles and abstracts for consideration by program committee. Application forms are available from John T. Martin, M.D., Chairman, Program Committee, Medical College of Ohio at Toledo, Box 6190, Toledo, Ohio 43614.

Scientific Exhibits—Application forms are available from B. B. Sankey, M.D., Executive Secretary, I.A.R.S., 3645 Warrensville Center Rd., Cleveland, Ohio 44122. There is no deadline for applications; however, applications received after November 1, 1976, are subject to exhibit space availability.

Technical (Commercial) Exhibits—Applications available from Charles B. Slack, Inc., Exhibit Manager, 6900 Grove Rd., Thorofare, New Jersey 08086.

C.M.E. Credit—This Continuing Medical Education offering meets the criteria for Category 1 credit (22 hours est.) for the Physician's Recognition Award of the American Medical Association.

On The History of Ideas in Anaesthesia

Tenth Annual Becton, Dickinson and Company Oscar Schwidetzky Memorial Lecture

LEROY D. VANDAM, MD*

Boston, Massachusetts

THIS convocation commemorates the 50 years over which the International Anesthesia Research Society has met annually to perpetuate its unique educational role in Anesthesia. Abiding by custom, a golden jubilee usually connotes a season of general joy and exultation for the good fortune we have had. But inevitably, as the span comprises more than half a lifetime, we are not only compelled to look back but tempted also to peer timorously into the future.

In tracing the history of the National Science Foundation, Detlev Bronk once observed: "The history of an institution is the tale of what people did; its future depends in part on the foundation they created." Thus, in the course of my remarks, some recounting of the people concerned in the development of the Society is justified, as is an affectionate nod in the direction of Oscar Schwidetzky for whom this memorial lectureship is named.

Mr. Schwidetzky's illustrious life in this country coincided with the founding by Francis Hoeffer McMechan and others, of the several regional groups that led ultimately to the formation of the International Society and the subsequent flowering of the specialty of Anesthesia. Earlier in 1900, Mr. Schwidetzky's arrival here from Germany, where he had been an apprentice instrument maker, also signaled the emergence of Anesthesia from the vacuous years following the initial use of nitrous oxide and ether. Probably only a few elders in this audience will recall Mr. Schwidetzky's gracious omnipresence at our anesthesia gatherings, where, as a stalwart of the Becton, Dickinson organization, he stood ready to transform our technical concepts into reality.

Thus, for example, he produced the malleable needle employed in continuous caudal and spinal anesthesia. Subsequently he came up with the prototype of the pediatric scalp vein needle in the form of a fine cannula that could be placed into an umbilical vein. His relations with the International Society were not merely coincidental, for the bond between physician and manufacturer was salubriously close in the early days, resulting in the formation of the National Anesthesia Research Society with both physician anesthetists and manufacturers as members. So did Mr. Schwidetzky function, and in 1956 he was honored for his cooperation by honorary membership in the International Society. At the time of award of an honorary Doctor of Laws degree in 1953 by Fairleigh Dickinson University, the citation read in part: "Probably at every place throughout this country where there are sick and wounded, and suffering persons —some product of his medical skill is relieving pain. . . ."

For this occasion, after considerable reflection, I set myself the goal of ascertaining those ideas that Anesthesia might have given to Medicine. What concepts or ideas have emanated from us? What are our utopian aims? Can we be styled as visionary or are we merely carried along by the tide? For the remainder of this address, I shall retrace the steps by which I arrived at the conclusions that came to mind.

At the outset, I found that I was not exceptionally innovative in my intention. More than a few milestone addresses have been

*Professor of Anaesthesia, Harvard Medical School; Anesthesiologist-in-Chief, Peter Bent Brigham Hospital, Boston, Massachusetts 02115.

Read at the 50th Congress of the International Anesthesia Research Society, March 14-18, 1976, Phoenix, Arizona.

published wherein the speaker elaborates on the contributions to Medicine of his specialty. This proves to be a comparatively easy exercise for Internal Medicine, as revealed by George Thorn's remarks in 1961, wherein he refers among other notable events to Joseph Lind's 1753 *Treatise on Scurvy*, a keystone in the formulation of modern concepts of nutritional and vitamin deficiency: to William Withering's account in 1785 of the medical uses of the foxglove, a classic in pharmacology; to Edward Jenner's *Inquiry into the Causes and Effects of the Variolae Vaccinae*, a fundamental contribution to immunology: successively then to Richard Bright, Thomas Addison, Robert Koch and Paul Ehrlich, and latterly to Sir Archibald Garrod's 1908 monograph on *Inborn Errors of Metabolism*, with notes on alkaptonuria, cystinuria, albinism, and pentosuria. Garrod advanced the concept that certain diseases of lifelong duration arise because an enzyme governing a single metabolic step is reduced in activity or missing altogether.

It is almost as convenient for Pediatrics to lay claim to certain benefits conferred upon mankind, as observed by essayist Harry H. Gordon. We are reminded of von Pirquet's skin test with tuberculin as a path to diagnosis, case finding, and now prophylactic therapy in tuberculosis; of the Schick test as a guide to routines of diphtheria immunization; to the discovery by Dutch pediatricians of gluten sensitivity as a cause for the celiac syndrome in childhood, with extension of their findings by English and other observers to the diagnosis and study of malabsorption syndromes at all ages; and in a more general sphere to the work of Howland, Holt, Marriott, Gamble, et al on the regulation of the intracellular and extracellular metabolism of water and electrolytes. None of the other specialties can lay claim to such extraordinary accomplishments in the specific treatment and prevention of disease, which comprise the essence of ecologic and physiologic medicine.

Perhaps I have already wandered too far from my main theme by referring to the cure and prevention of disease—Medicine's main thrust—for Anesthesia, by the very nature of its mandate, can lay no convincing claims in that direction. But I cannot refrain from going down this pathway for awhile. I have always believed that our highly specialized role in medical care was the chief reason for our nether ranking in the medical hierarchy, an impression confirmed by reading Iago Galdston's oration on the Birth and Death of Medical Specialties. His message has meaning for us all if we will only dwell upon it.

Galdston takes issue with the prevalent concept of modern medicine as a continuous and accelerated detachment of various specialties from the main trunk of medical practice. Rather, he points out that specialism had its origins in antiquity, for it was never more specialized than in Egypt. "Each physician applies himself to one disease only and not more," according to Herodotus. "Some physicians are for the eyes, others for the head, others for the teeth, others for the intestines and others for internal disease."

Are those observations not reminiscent of the current trend toward collateralization away from the main vessel of Anesthesia? Galdston reasons that specialization is not concomitant with nor is it in itself a gauge of the advancement of medicine. "Specialties rise and fall in importance, some disappearing from the scene entirely. Indeed, the long view of the history of science reveals a pattern of periodic diversifications in interest and knowledge, that is—of specialization, followed by periods wherein the synthetic unification of knowledge is achieved. Science is never more innately consonant and rewarding than during its unitary stage." I would like to fancy that some of the ideas generated by Anesthesia fall within the unification process, an argument I shall proceed to.

Anesthesia as a specialty differs from all others in that its origins lie not in the conquest of disease—its causation, prevention, or treatment. Rather it rose upon the scene quite late, beginning (in the 18th century) with the work of biochemists, their recognition of oxygen and carbon dioxide as elements in the life process, and the use by several physicians of gases and vapors in the treatment of disease. Certain keen observers, as typified by Davy and Hickman, reasoned that some of these vapors might be useful in relieving the pain of surgical operations. These were the very first ideas! Elsewhere, your speaker has observed that certain social events and changes in attitude toward man and the relief of pain led to the eventual introduction, in the 1840s, of ether, nitrous oxide, and chloroform. Owsei Temkin notes:

"Sociologists of science have cited in evidence for social causation the multiple appearance of the same discovery—'multiples' in the language of Robert Merton. The independent use of anesthesia by Long, Wells, and Morton is a well known medical example. Though discoveries are not necessarily ideas, both are spoken of as being 'in the air' or ripe for their time."

Now, as we have come a little closer to matters of ideas and discovery, further definition is essential. You may be surprised to learn, as was I, that there is not only a journal devoted to the history of ideas but recently the appearance of a periodical concerned solely with medical hypotheses. In the opening essay of Volume I of the Journal of the History of Ideas, Arthur O. Lovejoy notes: "Whatever other definitions of man be true or false it is generally admitted that he is distinguished among the creatures by the habit of entertaining general ideas. Like Brer Rabbit he has always kept up a heap o' thinking. And ideas are the most migratory things in the world." Furthermore, "One of the safest (and most useful) generalizations resulting from a study of the history of ideas is that every age tends to exaggerate the scope or finality of its own discoveries, or rediscoveries,—to be so dazzled by them that it fails to discern clearly their limitation. . . ." Again it is useful for us to reflect upon this timely observation. Also note that Lovejoy cannot resist using the terms "ideas" and "discovery" interchangeably.

In another analysis, Peter Caws examines the Structure of Discovery. Logical analysis, he avers, is not appropriate to inquiry into the way in which claims to scientific knowledge originate. "Rather, questions about origins are said to belong to the context of discovery, requiring a different kind of logic. The devising of hypotheses is ascribed to genius, intuition, imagination, chance or any number of other extralogical processes. One of the tactics most often used by proponents of the mystique of genius who are always bandying about terms like creativity, insight, ripeness and so on, is the recounting of tales about moments of enlightenment in the lives of great scientists."

While we are too close to the present to discover the genius amongst us, would you not agree that it was something akin to a combination of genius and insight in an aura of ripeness that led the vanguard first to suggest the possibility of relieving the pain of surgical operations—then to demonstrate the means by which it could be done? Among the vanguard we would all cite Humphry Davy, Henry Hill Hickman, Crawford W. Long, Horace Wells, and William T. G. Morton. An analysis of their individual discoveries, as in all matters of this kind, as Caws writes, "shows that in practically every case the individual acted as the catalyst for a complex process in which many other individuals played a role. This need not be taken to mean that no credit is due the individual for having advanced his science in a particular way at a particular time but it does mean that (probably) no individual has been indispensable to the advance of science in general."

So far as perceiving ideas derived from Anesthesia is concerned, one should recall Newton's celebrated remark about "standing on the shoulders of giants." Writes Caws, "It serves to remind us that the development of science is a stepwise process; nobody starts from scratch and nobody gets very far ahead of the rest. At any point in history there is a range of possible discovery; the trailing edge of the range is defined by everything known at the time (I overlook the fact that people are constantly 'discovering' what is known—which blurs the image somewhat) and the leading edge is a function of what is already known, together with variables representing available instrumentation, the capacity of human brains, and so on."

In the context of Caws' analysis, can we say that we have hatched any epochal discoveries or ideas since the first demonstrations? It is not a simple matter to answer this question, for our discoveries, if any, resulting from the research we have done, reside in the realm of clinical rather than physiologic medicine. A. R. Feinstein has raised the question: What kind of basic science for clinical medicine? He explains that the practice of medicine entails two kinds of decisions: the explanatory decisions involving the naming, mechanisms, and causes of disease; and the managerial decisions for therapeutic interventions—to prevent or alter disease. Wouldn't you agree that our thrust has been almost entirely in the managerial sphere?

We cannot claim to have explained much in relation to the foundations of our practice—the mechanisms of narcosis and pain. Progress in these areas is being made nevertheless, as others have begun to collect the

data necessary for establishment of the appropriate hypotheses. Moreover, anesthesiologists are working on the leading edge of discovery in these areas. Managerially, we in Anesthesia cannot accept the praise, if any is due, for synthesizing the many controversial anesthetics that have been introduced to practice. As a rule we receive new compounds from the manufacturers, then discover what they are all about in broad, unsupervised clinical trials. In this respect, perhaps, we have made little progress since the 1840s.

The evolution of technics of balanced anesthesia represents a considerable step forward, inasmuch as the clinical phenomenon designated as anesthesia has been dissected into its components: analgesia, loss of consciousness, and muscle relaxation. But here, too, Claude Bernard first pointed out the benefits to be derived from giving morphine before anesthetization, while George Crile, Senior, combined the attributes of regional and general anesthesia in order to combat the development of surgical shock, according to his anoci-association theory. We were then given the short-acting intravenous barbiturates, and several varieties of neuromuscular blockers to complete the ingredients of modern balanced anesthesia. Several anesthetists deserve credit for hastening the process: J. S. Lundy and R. M. Waters for introduction of the barbiturates and Johnson and Griffith for their daring in giving tubocurarine to man. These people rode on the leading edge of discovery!

It occurs to me that balanced anesthesia, and the detailed study of the drugs used in its format, probably represent the greatest advance in the managerial aspects of anesthesia. Although the mortality resulting from anesthesia probably was enhanced at first, subsequent experience with the use of multiple agents may have led to an apparent decrease in both anesthetic morbidity and mortality. As a result, all of the new potent general anesthetics are used in balanced technics, with a short-acting barbiturate employed for induction and attainment of unconsciousness, nitrous oxide given for its concentration and second gas effects as well as a mainstay for analgesia, and neuromuscular blockers to circumvent the deeper planes of general anesthesia required for good muscle relaxation.

If anesthetic mortality has been reduced thereby, can we not proclaim that we have made a major contribution to preventive or ecologic medicine—the reduction in hazard of a major environmental threat—general anesthesia? The environmental threat to those who work in an atmosphere of anesthesia is also under scrutiny. But in the realm of ideas or discovery we ought not to be praised for making our practice safer, any more than the cardiologist should be cited for the more proficient use of digitalis, for a long time a little-recognized but leading cause of sudden death in patients treated for heart disease.

A few other pharmacologic events come to mind, not that we were the innovators, but we were the practitioners who allowed surgical patients to benefit from these concepts. I recall all that has been learned concerning the uptake, distribution and metabolism of anesthetics, beginning with measurements on ether by H. W. Haggard in the twenties, and the many subsequent studies on other anesthetics, employing quantitative technics. S. S. Kety, working in an atmosphere of anesthetic thought at Pennsylvania, figured out the mathematic equations underlying transport, while it remained for basic scientists in Anesthesia to demonstrate the actuality in man—again along the leading edge of discovery.

Parenthetically, anesthesiologists could lay claim to being among the first to take advantage on a large scale of the human volunteer in experimentation, thereby permitting the action of drugs to be assayed in the absence of disease and surgical stress, apart from considerations of species differences. Conversely, we wouldn't want to bear the onus for the ethical abuses in human experimentation that have led to much-needed regulation and to protection of human subjects, whether volunteer or patient.

A few more general ideas come to mind—all in the pharmacologic arena: the realization that inhalation anesthetics are not after all inert, rather that they are metabolized in varying degree, sometimes to toxic metabolites—either hepatotoxic or nephrotoxic—their sites of metabolism and excretion, and with adverse effects on embryonic tissues. Inadvertently, we have broadened the horizons of pharmacogenetics by the use of xenobiotics such as succinyldicholine, discovering that there are several kinds of genetically transmitted abnormal plasma cholinesterases. A related iatrogenic disease has been rediscovered—malignant hyperthermia. Remember Caws' remark that people are constantly rediscovering what is

already known? Finally, so far as clinical pharmacology may profit from our trials, we have added considerably to the knowledge of drug interactions and in general to the epidemiology of iatrogenic disease.

My remarks thus far have touched upon a few ideas and discoveries in which we have played a role, without necessarily receiving recognition, simply because we work in the managerial rather than the descriptive sphere of medicine. However, transcending all of these accomplishments is one inalienable characteristic of anesthetic practice—that is our ability, willingness, and courage in manipulating man's internal environment, the *milieu intérieur* of Claude Bernard and the homeostatic systems of Walter B. Cannon. I allude to the deliberate control of respiration, circulation, body temperature, and fluid and acid-base balance.

The lessons learned from these excursions or incursions into the physiology of man have had wide-reaching consequences for clinical medicine: the treatment of pulmonary disease, heart disease, neurologic ailments, and allied surgical interventions. With this new power, we had to devise the means to assess quantitatively what we were doing, beneficially or otherwise, to the homeostatic systems of the body. Step by step, in the remaining paragraphs of this discourse, I shall enlarge upon this thesis. As an aside, I call your attention to the recent publication of the proceedings of a conference on Anesthesiology, held in Washington under the auspices of the National Institute of General Medical Sciences, entitled: "Anesthesiology, Its Expanding Role in Medicine." The substance of this report parallels that whereof I speak.

On respiration first! It is interesting to find that in the last half of the 19th century physiologists were using positive-pressure ventilation in the management of the open thorax and they were, of course, aware of the neuromuscular-blocking properties of tubocurarine. Meltzer and Auer in the teens then demonstrated the feasibility of apneic oxygenation in the dog. That anesthetists were slow to adopt these measures is simply a reflection of a contention made before, that Anesthesia had to await the development of Surgery, not only to recruit people unto itself but to take advantage of technics already proven in the laboratory.

Arthur E. Guedel, in the thirties, probably with the encouragement of Ralph M. Waters, was the first to define the means by which respiration could be controlled in man, either by increasing the depth of ether anesthesia, through hyperventilation, or by a combination of both. Pharmacologic control of respiration, he said, led to better operating conditions within the abdomen. Control of respiration became commonplace after the introduction of cyclopropane, and mechanical ventilation of the lungs mandatory following the use of tubocurarine. The proliferation of endotracheal technics arose out of necessity.

But let us reflect on the consequences in terms of general medical utility and treatment of a host of illnesses. A variety of respiratory patterns emerged along with the mechanical equipment to do the job: pressure- or volume-controlled ventilation; intermittent positive-pressure breathing; continuous positive-pressure breathing, positive end-expiratory pressure and intermittent-demand breathing. The box was opened in the effects on ventilation-perfusion ratios, secondary effects on circulation, emergence of iatrogenic phenomena—pneumothorax, tracheal damage, and problems in weaning from controlled ventilation. A vast clinical literature appeared, largely in the managerial sphere, with observations from both basic scientists and clinical investigators in Anesthesia.

New light was cast on the effects of mechanical control of ventilation in respect to small-airway dynamics, the relation between central and peripheral chemoreceptor control of respiration, details of chest and lung compliance, and the consequences of hyper- or hypoventilation in relation to oxygen or carbon dioxide. One could go on and with a myriad of citations while cogitating on the benefits derived in the treatment of disease: pneumonia, pulmonary embolism, coma resulting from poisoning, chest trauma, respiratory-tract burns, aspiration of gastric contents, tetanus, myasthenia gravis, drowning, the postsurgical lung, and the infant and so-called adult respiratory distress syndromes.

A secondary bonus accrued in the management of intracranial disease: anesthesia for intracranial surgery; treatment of stroke, seizures, and head trauma. The pattern and volume of ventilation strongly influence intracranial pressure, the distribution of water between the several compartments, and the course of blood flow. Cerebral blood flow and its partition between normal and diseased tissues is as much influenced by respiratory-induced changes in acid-base balance as by the mean level of blood pressure.

Anesthesiologists have worked on the leading edge of investigation—in the quantitative assessment of the effects of pulmonary ventilation on distribution of cerebral blood flow—an eminent contribution to physiologic medicine. As might have been anticipated, in spite of our facility in altering the respiratory environment, we have rediscovered a basic tenet that maintenance of normal blood levels of oxygen and carbon dioxide is for the better in practically every situation.

As you know, it is hardly possible to separate the physiologic effects of alterations in respiration or circulation, but let us now observe how anesthesiologists have at times taken over control of the circulation. Beginning with the advocacy by Harvey Cushing of the need to measure blood pressure during anesthesia, anesthetists for the first half of this century, in this country at least, devoted much of their clinical effort and research to maintenance of normotension during anesthesia. Then as a byproduct of neurosurgery, W. J. Gardner and D. F. Hale found that lowering of blood pressure by deliberate blood-letting provided better conditions during intracranial operations, at least in the crisis situation.

As a John Clover lecturer in 1950, John Gillies was then impelled to take as his theme, "Anaesthetic Factors in the Causation and Prevention of Excessive Bleeding During Surgical Operation." As the concept was presented, why not control the blood pressure by one of several means, mechanical or pharmacologic, to diminish blood loss and improve operability—via the hypotension resulting from spinal anesthesia, use of ganglionic blocking agents or peripheral vasodilators—and positioning of the part to be operated upon above the level of venous pressure. So was deliberate hypotension conceived, with more than a few complications at first but ultimately with real benefit as soon as the effects on regional circulation in brain, heart, kidneys, and liver were discerned. Blood flow in normal cerebral vessels accommodates to changes in mean blood pressure in a range between 60 and 180 torr. So is it the rule for the coronary artery circulation.

A tertiary benefit emanating from a safe level of hypotension lay in the decreased work of the heart against an afterload, hence less demand for oxygen. Increase in heart rate and enhancement of myocardial contractility also increase the work of the heart. These principles now guide the anesthesiologist in the intraoperative management of patients with coronary arteriosclerosis and myocardial ischemia; a modest blood pressure, slow heart rate, and muted inotropic activity are beneficial. And the impact has not been lost on Cardiology, where dissecting aneurysm, myocardial ischemia and infarction or heart failure may be alleviated by the use of modest degrees of controlled hypotension via an appropriate combination of alpha- and beta-sympathetic agonists and antagonists.

And there is at least one more homeostatic system that we manipulate willingly, sometimes unwittingly, during the course of anesthesia, that is the body temperature. Here we dare not transgress in both directions for we fear the ravages of hyperthermia. In the late 1930s, deliberate cooling of the body was first practiced in an attempt to control the spread of inoperable malignant tumors, abandoned, then resurrected a decade later in conjunction with open-heart surgery. The idea was to lower the oxidative needs of the brain during a brief span of total circulatory occlusion. Much was learned of the physiology of deep hypothermia in the realm of metabolism of tissues, and the dangers thereof. Total body hypothermia became a little too much to handle, but the principle remains in relation to individual organs, where the heart is cooled during bypass surgery, kidney temperature lowered before transplantation, the cerebrum protected by deep hypothermia during complex cerebrovascular operations, and the traumatized brain protected by maintenance of normothermia.

It is high time to conclude this oration. If my analysis can be taken as correct, Anesthesia has conferred a great many benefits on physiologic medicine, not truly in the realm of ideas or discovery but in the managerial sphere. We could not have been held responsible for the introduction of Anesthesia because the discovery preceded our birth, nor have we as scientists explained the mechanism of narcosis or pain. As a result of our investigations, however, and the utilization in combination of new compounds given us, we may have significantly decreased the epidemiologic hazard of surgical anesthesia. In the course of so doing, moreover, our ability, daring, and inventiveness in manipulating respiration, the circulation, and body temperature, which no other physicians had had the opportunity to explore

so thoroughly, have had broad implications for medicine, in the care of the critically ill. This transpires not only in the operating room but in emergency wards, recovery rooms, and the many kinds of intensive care facilities now extant.

We may derive a measure of solace in the knowledge that even though anesthesia may one day become so safe, through the application of better agents and predictive monitoring devices, as to warrant the attention mostly of technically able personnel supervised by physicians—that we shall nevertheless still have a role to play in the intensive care of critically ill patients everywhere. This is a trend resented or denied by some of the older generation of anesthetists, but we are witnessing its rapid evolution in the aspirations of many young people training in Anesthesia today. They are attracted to the field mainly by the prospect of caring for people who are desperately ill. And the reward comes from witnessing recovery and restoration of people to a meaningful existence as contrasted with what at one time might have been the fatal outcome.

BIBLIOGRAPHY

Black EA, Deming PA: Anesthesiology: its expanding role in medicine: a research conference report. DHEW Publication # (NIH) 76-918, 1975

Caws P: The structure of discovery. Science 166: 1375-1380, 1969

Feinstein AR: What kind of basic science for clinical medicine? N Engl J Med 283:847-852, 1970

Galdston I: The birth and death of specialties. JAMA 167:2056-2061, 1958

Gordon HH: Basic contributions to medicine by research in pediatrics. JAMA 177:748-754, 1961

Lovejoy AO: Reflections on the history of ideas. J Hist Ideas 1:3-23, 1940

Seldon TH: Anesthesia and Analgesia—50 years of publication. Anesth & Analg 50:571-577, 1971

Temkin O: The historiography of ideas in medicine, Modern Methods in History of Medicine. Edited by E Clarke. London, Athlone Press, 1971, chapter 1

Thorn GW: Basic contributions to medicine by research in internal medicine. JAMA 177:739-747, 1961

Vandam LD: Early American anesthetists: the origins of professionalism in anesthesia. Anesthesiology 38:264-274, 1973

CORRECTION

May-June 1976 issue, page 424: Caption under photograph (bottom of page) should read: Dr. John H. A. Lawrence, President, Canadian Anaesthetists' Society, honored guest at the 50th Congress Golden Anniversary Luncheon.

Influence of Pancuronium on Potassium Efflux Produced By Succinylcholine

HALAPPA N. KONCHIGERI, MD*
CHENG-HIN TAY, MD†
Chicago, Illinois‡

Serum potassium (K^+) levels were measured after thiopental, succinylcholine, pancuronium, and pretreatment with pancuronium prior to succinylcholine, in 100 patients divided into 4 groups of 25 patients each. Significant increases in serum K^+ were found after succinylcholine (1 mg/kg). Administration of pancuronium in small doses (20 μg/kg) prior to succinylcholine (1 mg/kg) was effective not only in complete prevention of serum K^+ elevation but also produced consistent decrease in serum K^+ concentration below control values. Both thiopental and pancuronium produced moderate fall in serum K^+ levels. Our observations indicate that pretreatment with pancuronium may play a beneficial role in patients at risk from succinylcholine hyperkalemia.

A SMALL but significant increase in plasma potassium (K^+) level (0.25 to 0.8 mEq/L) following succinylcholine administration has been observed in normal anesthetized patients. But extraordinary increase of K^+ (massive hyperkalemia) has been witnessed in patients with extensive burns,[1] massive trauma,[2] neuromuscular disorders,[3-5] and tetanus,[6] leading to serious, even fatal cardiac arrhythmias and cardiac arrest. These reports have induced great interest in searching for preventive measures against succinylcholine hyperkalemia. Some investigators[5,7-10] have studied the influence of pretreatment with d-tubocurarine and gallamine before succinylcholine administration and found beneficial effects in attenuation of K^+ efflux after succinylcholine. These studies prompted us to pursue the course further in this area and study the effect of pretreatment with pancuronium on serum K^+ changes produced by succinylcholine.

MATERIALS AND METHODS

Serum K^+ levels were measured during induction of anesthesia in 100 patients undergoing various elective surgical procedures. Patients were of both sexes, ranged in age from 17 to 87 years (average 44.7), and were of ASA physical status I or II. All were free from neuromuscular, cardiovascular, acid-base, and electrolyte disorders.

Preoperative laboratory work-up included hemogram, urinalysis, electrolyte measurements, chest x-rays, and ECG.

Premedication.—Patients received atropine (0.4 to 0.6 mg) with or without the combination of morphine (0.1 mg/kg) or meperidine (1 mg/kg) IM approximately 1 hour before anesthetic induction.

Anesthetic Management.—The 100 patients were divided into 4 groups of 25, according to technic of induction. All patients received sodium thiopental (3 to 5

*Assistant Professor.
†Instructor.
‡Department of Anesthesiology, Abraham Lincoln School of Medicine, University of Illinois Hospitals, Chicago, Illinois 60612.

Paper received: 8/25/75
Accepted for publication: 10/25/75

mg/kg), but patients in group I received no muscle relaxants during the study period, group II was given succinylcholine (1 mg/kg) prior to endotracheal intubation, group III received pancuronium (0.1 mg/kg), and group IV received pancuronium (20 μg/kg) 3 minutes before administration of succinylcholine (1 mg/kg). The trachea was sprayed with 4% (4 ml) lidocaine by LTA Kit® before placement of the endotracheal tube in all but group I patients. Anesthesia was maintained with 70 percent N_2O and O_2, supplemented with either divided doses of thiopental sodium or fentanyl during the observation period. Respiration was either assisted or controlled to maintain the adequacy of ventilation. Monitoring included pulse rate, blood pressure, respiratory rate, temperature, and ECG.

Measurements.—Blood samples (venous) for K^+ estimation were obtained through a large-bore cannula placed in a vein from the forearm opposite the one in which induction agents were administered. Blood samples were drawn into heparinized syringes immediately before induction of anesthesia, and 1, 2, 3, 4, 5, 6, 7, 10, and 15 minutes after, the administration of succinylcholine (groups II and IV), pancuronium (group III), and sodium thiopental (group I). During the sampling period, fluid administration was limited to minimal amount (less than 50 ml) of either 5% dextrose or normal saline solution. Surgical incision was delayed until the completion of the sampling period. Blood gases were analyzed in 8 patients of each group, selected at random, to monitor the adequacy of ventilation and oxygenation.

Serum K^+ was measured by an Instrumentation Laboratories Flame Photometer Model 343. Blood gases (Pao_2 and $Paco_2$) and pH were determined by a Radiometer Digital Acid-base Analyzer.

Statistical comparisons of the serum K^+ changes were made using Student's *t*-test for paired data. A probability of 0.5 percent or less ($p<0.05$) was considered significant.

RESULTS

Thiopental administration (group I) produced a sustained fall in serum K^+ levels during the entire observation period. However, the changes reached significant level ($p<0.05$) only at 1 and 4 minutes of the postinduction period. Mean maximum change was −6.5% of the control value (table).

TABLE
Serum Potassium (mEq/L ± SD) Before and After Induction Agents

Group and agents	Preinduction (control)	Minutes after induction								Maximum change	
		1	2	3	4	5	7	10	15	Absolute	Percent
Group I Thiopental	3.53 ±0.31	3.30 ±0.36	3.34 ±0.39	3.38 ±0.32	3.31 ±0.29	3.34 ±0.29	3.34 ±0.29	3.32 ±0.33	3.39 ±0.32	−0.23	−6.5
		<0.05	>0.05	>0.05	<0.05	>0.05	>0.05	<0.05	>0.05		
Group II Thiopental + succinylcholine	3.56 ±0.30	3.52 ±0.40	3.99 ±0.90	3.81 ±0.30	3.82 ±0.49	3.80 ±0.49	3.76 ±0.45	3.66 ±0.45	3.64 ±0.47	0.43	12.0
		>0.05	<0.05	<0.05	<0.05	<0.05	>0.05	>0.05	>0.05		
Group III Thiopental + pancuronium	3.80 ±0.50	3.40 ±0.40	3.49 ±0.30	3.60 ±0.48	3.60 ±0.46	3.50 ±0.36	3.50 ±0.50	3.50 ±0.35	3.50 ±0.30	−0.41	−10.7
		<0.01	<0.01	>0.05	>0.05	<0.05	>0.05	<0.05	<0.05		
Group IV Thiopental + pancuronium + succinylcholine	3.81 ±0.49	3.49 ±0.45	3.58 ±0.42	3.66 ±0.43	3.66 ±0.46	3.68 ±0.58	3.69 ±0.42	3.69 ±0.46	3.70 ±0.43	−0.31	−8.1
		<0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05		

After succinylcholine administration (group II), there was a prompt rise in serum K^+ in 2 minutes, which remained significantly ($p<0.05$) elevated between 2 and 5 minute intervals. Mean changes in K^+ values in group II were significantly higher than those in group I. Peak rise in K^+ level was 12 percent (table).

Pancuronium (group III) produced variable decrease in serum K^+ concentration, and changes were significantly lower than the control values during 1, 2, 5, 10, and 15-minute sampling periods. No significant difference between groups III and II was found. Mean maximum drop in serum K^+ was 10.7% (table).

Pretreatment with pancuronium before administraton of succinylcholine (group IV) resulted not only in complete prevention of rise in serum K^+ concentration but also in a milder degree of drop in serum K^+ levels. The results were not significantly different from control values but were highly significant ($p<0.001$) in comparison with group II (table).

Fasciculations developed in all 25 patients who received succinylcholine (group II). Fasciculations were completely prevented in 23 patients by pancuronium pretreatment (group IV). Mean changes in heart rate of −15 to +20 per minute, and systolic blood pressure of −15 to +30, were recorded during the study period. Mean values of blood-gas results were: Pao_2, 153 torr; $Paco_2$, 38 torr; pH, 7.41.

DISCUSSION

In 1956, Paton[11] demonstrated that the release of potassium from the isolated perfused gastrocnemius cat muscle after succinylcholine was about 1% of the potassium content of the muscle. He also confirmed that the muscle was the source of this potassium in his experiments. In intact animals, there was a substantial (as much as 30%) increase in serum K^+ after succinylcholine and decamethonium administration.[8,9]

Succinylcholine, acting at the motor endplate receptor site, decreases the transmembrane potential and increases the ionic permeability of Na^+ and K^+ in the process of depolarization. Rapid influx of Na^+ is followed by efflux of intracellular K^+, producing elevated serum K^+ levels with an average increase of 0.5 mEq/L in subjects with normal muscle.[12-14]

Hyperkalemia following administration of succinylcholine in patients with extensive burns, massive trauma, and neuromuscular disorders involving loss of motor function with resultant atrophy is believed to be the result of release of unusual amounts of K^+ from abnormal skeletal muscle. Gronert and colleagues[15] reported a twentyfold increase in efflux of K^+ from the denervated muscle, while the efflux from normal muscle remained unchanged after succinylcholine. These observations are indicative of a change in receptor properties of the denervated muscle. The receptor area of denervated muscle progressively enlarges, until the entire surface membrane of muscle fiber develops greater sensitivity to a chemical depolarizer. Succinylcholine depolarization of this entire supersensitive membrane will lead to massive release of intracellular K^+ into the circulation, producing abnormally high levels of serum $K.^{+13-15}$

In contrast to depolarizing muscle relaxants, nondepolarizing muscle relaxants (d-tubocurarine and gallamine) are found to produce either no change or a decrease[7,9,16] in serum K^+ levels, both in man and animal studies. Bali and associates[16] observed that decrease in serum K^+ concentration was more marked after pancuronium than after the other 2 nondepolarizing relaxants. Gallamine and d-tubocurarine, when administered in small doses before succinylcholine, have been shown to effect beneficial attenuation of serum K^+-level rise.[5,7-9,14,15] Although the exact mechanism for these effects is not well established, it is quite possible that nondepolarizing relaxant drugs provide stabilization of muscle-cell membrane, decrease the number of depolarizations at the motor end-plate, and help in intracellular influx of serum K^+.[16]

The present investigation indicates that barbiturates produce a sustained fall in serum K^+ levels. This finding is consistent with observations of other investigators.[17,18] There was an immediate rise in serum K^+ concentration after succinylcholine, which peaked at the 2-minute interval and remained higher than the preinduction value during the entire sampling period. However, elevation in serum K^+ levels were significant only between 2 and 5 minutes of the postrelaxant period. Studies[17] on the relationship between the induction agents and K^+ efflux due to succinylcholine have revealed that there was a greater elevation of serum K^+ levels with halothane than with thiopental when these agents were used for induction. At present, no explanation is

available for the changes related to induction agents.

Pancuronium kept the serum K^+ levels consistently lower than the control values; similar findings have been witnessed by other investigators.[16] An interesting observation was that pretreatment with pancuronium prior to succinylcholine (group IV) was successful, not only in complete prevention of the rise in serum K^+ levels, but also in maintaining the K^+ concentrations in serum below the control values during the study period.

Acidosis or alkalosis can significantly affect serum K^+ measurements.[19,20] In the present study, arterial blood gas and pH measurements were within normal limits and had no effect on serum K^+ determinations.

We conclude that pancuronium pretreatment before succinylcholine administration results in complete attenuation of the rise in serum K^+ concentration. Similar measures may play a beneficial role in patients at risk from succinylcholine hyperkalemia. However, further studies are needed to confirm our viewpoint.

ACKNOWLEDGMENT

We wish to express our thanks to Drs. K. Patel, S. Akkineni, and M. T. Shin for their valuable help in this study.

REFERENCES

1. Schaner PJ, Brown RL, Kirksey TD, et al: Succinylcholine-induced hyperkalemia in burned patients—1. Anesth & Analg 48:764-770, 1969

2. Mazze RI, Escue HM, Houston JB: Hyperkalemia and cardiovascular collapse following administration of succinylcholine to the traumatized patient. Anesthesiology 31:540-547, 1969

3. Tobey RE: Paraplegia, succinylcholine and cardiac arrest. Anesthesiology 32:359-364, 1970

4. Tobey RE, Jacobsen PM, Kahle CT, et al: The serum potassium response to muscle relaxants in neural injury. Anesthesiology 37:332-337, 1972

5. Cooperman LH: Succinylcholine induced hyperkalemia in neuromuscular disease. JAMA 213:1867-1871, 1970

6. Rotl F, Wuthrich H: The clinical importance of hyperkalemia following suxamethonium administration. Br J Anaesth 41:311-316, 1969

7. Klupp H, Kraupp O, Honetz N, et al: Über die Freisetzung von Kalim aus der Muskulatur unter Einwirkung einiger Muskelrelaxantien. Arch Int Pharmacodyn 98:340-354, 1954

8. Weintraub HD, Heisterkamp DV, Cooperman LH: Changes in plasma potassium concentration after depolarizing blockers in anaesthetized man. Br J Anaesth 41:1048-1052, 1969

9. Worth KC, Wetstone D, Martin WE, et al: Hypokalemia during anesthesia: the effects of d-tubocurarine, gallamine, succinylcholine, thiopental, and halothane with or without respiratory alkalosis. Anesth & Analg 52:522-528, 1973

10. Dhanaraj VJ, Narayanamurthy J, Sitadevi C, et al: A study of the changes in serum potassium concentration with suxamethonium using different anaesthetic agents. Br J Anaesth 47:516-519, 1975

11. Paton WDM: Mode of action of neuromuscular blocking agents. Br J Anaesth 28:470-480, 1956

12. Katz B: Nerve, Muscle, and Synapse. New York, McGraw Hill, 1966

13. Vaughan RS, Lunn JN: Potassium and anaesthetics. Anaesthesia 28:118-131, 1973

14. Gronert GA, Theye RA: Pathophysiology of hyperkalemia induced by succinylcholine. Anesthesiology 43:89-99, 1975

15. Gronert GA, Lambert EH, Theye RA: The response of denervated skeletal muscle to succynlcholine. Anesthesiology 39:13-22, 1973

16. Baliga IM, Coppel DL, Dundee JW: The effect of non-depolarizing muscle relaxants on plasma potassium. Br J Anaesth 47:505-507, 1975

17. Stovner J, Endersen R, Bjelke E: Suxamethonium hyperkalemia with different induction agents. Acta Anaesth Scand 16:46-50, 1972

18. Baliga IM, Dundee JW, Assaf RAE: Immediate changes in plasma potassium induced by intravenous induction agents. Br J Anaesth 45: 1238, 1973

19. Scribner BH, Fremont-Smith K, Burnell JM: The effect of acute respiratory acidosis on the internal equilibrium of potassium. J Clin Invest 34:1276-1285, 1955

20. Keuskamp DHG: Hyperventilation und Gehirnhypoxie. Anaesthesist 14:204-210, 1965

Physostigmine Reversal of Sedation in Parturients

DOUGLAS B. SMITH, MD*
RICHARD B. CLARK, MD†
STACY R. STEPHENS, MD
ROBERT L. SHERMAN, MD‡
MARSHALL L. HYDE, MD§

Parturients in whom meperidine HCl, propiomazine HCl, and scopolamine were used for analgesia and amnesia in labor and delivery were studied to determine the efficacy and safety of physostigmine reversal after delivery. Of a total of 120 patients, 108 received physostigmine salicylate at the completion of episiotomy closure, awakening in an average of 7.5 minutes compared with 137.8 in 12 controls. Physostigmine appears to be a safe, rapidly effective agent for reversing the prolonged somnolence of this sedation regimen.

SMALL doses of scopolamine combined with various analgesics and tranquilizers have been found useful for pain relief during labor.[1]** Small doses of the phenothiazine, propiomazine, added as a narcotic adjuvant to minimal doses of meperidine, produce a sedated, amnesic, and comfortable patient. While our patients have been generally satisfied with this regimen, their one complaint is that it is several hours before they are reactive enough to talk to their families and see their babies.

Encouraged by reports of the safety and effectiveness of physostigmine,[2-11] an anticholinesterase capable of reversing the central effects of scopolamine and a variety of other drugs that may have anticholinergic activity, we have found Antilirium®, the salicylate of physostigmine, useful in providing more rapid awakening of the sedated parturient.

MATERIALS AND METHODS

For clinical and statistical comparisons, physostigmine was given IV at the completion of episiotomy closure to a series of 108 normal parturients (mean age 24.2 years, mean weight 66 kg, 1st postpartum day) given fractional doses of meperidine HCl, propiomazine HCl, and scopolamine for analgesia and amnesia. When active labor began, the 1st dose, comprising meperidine (50 mg), propiomazine (20 mg), and scopolamine (0.6 mg), was given IV. Additional increments, usually one-half the original dose, were given IV as needed during labor. The total dosage and the last dose of each drug given were recorded (table).

Half of each group were primigravidas. Either pudendal block or local infiltration

**Actually, since the development of morphine-scopolamine "twilight sleep" at the turn of this century. Ed.

*Clinical Instructor, Department of Obstetrics and Gynecology.

†Professor, Departments of Anesthesiology and Obstetrics/Gynecology.

‡Clinical Assistant Professor, Department of Obstetrics and Gynecology.

§Clinical Instructor, Department of Obstetrics and Gynecology.

Departments of Obstetrics and Gynecology, Sparks Regional Medical Center, Fort Smith, Arkansas 72901 and the University of Arkansas for Medical Sciences, Little Rock, Arkansas.

Reprint requests to: Douglas B. Smith, M.D., 408 S. 16th Street, Fort Smith, Arkansas 72901.

Paper received: 11/18/75

Accepted for publication: 12/9/75

TABLE

Drug Dosage and Awakening Time in Control and Study Patients

(Figures represent mean ± 1 SD)

Patients	Control group (N = 12)	Study group (N = 108)
Total dose meperidine, mg	100 ± 33.7	101.3 ± 38.9
Last dose meperidine, mg	29.2 ± 9.7	30.2 ± 10.4
Total dose propiomazine, mg	40 ± 13.5	40.2 ± 15.35
Last dose propiomazine, mg	11.7 ± 3.9	12.3 ± 4.2
Total dose scopolamine, mg	1.1 ± 0.4	1.0 ± 0.3
Last dose, scopolamine, mg	0.35 ± 0.1	0.4 ± 0.1
Physostigmine, mg	—	2.0 ± 0.6
Time from episiotomy closure to awakening, minutes	137.8 ± 49.6	7.5 ± 12.8

anesthesia was used for delivery. Physostigmine was given immediately after closure of the episiotomy in a dose double the amount of scopolamine used during labor, as recommended by others.[5,7,11] The time from episiotomy closure until the patient was coherent enough to give her home phone number was recorded as the awakening time, and the results were compared with those of 12 controls (mean age 22.6 years, mean weight 66.7 kg), not given physostigmine.

Arterial blood pressures and peripheral pulse rates were recorded immediately after episiotomy closure, before physostigmine administration and recorded at 2, 4, 6 minutes and 1, 2, and 24 hours after injection. In addition, such physostigmine side effects as nausea, vomiting, irregular pulse, salivation, and the complaint of being cold were noted (although temperatures were not recorded as part of the study).

RESULTS

Mean total doses of meperidine, propiomazine, and scopolamine were similar in the 2 groups (table). This dosage schedule gave satisfactory analgesia and amnesia in all patients. Mean awakening time following episiotomy closure in the physostigmine group was 7.5 ± 12.8 minutes, compared with 137.8 ± 49.6 minutes in the control group, a highly significant difference ($p<0.001$, Student's t-test).

Mean blood pressure was similar in both groups except at 60 and 120 minutes, when it was slightly lower in the physostigmine group; however, this slight drop was not believed clinically significant. While the mean pulse rate fell after episiotomy closure in each group, the drop was significantly greater in the study group at each time interval, falling from a mean of 91.8 ± 14.7 torr before physostigmine to a low of 75.6 ± 10.9 after 60 minutes. After 24 hours, blood pressures and pulse rates were similar in both groups.

In the study group, the mean 1-minute Apgar score was 8, with a range of 3 to 10, and 10.2% with a score below 7. In the control group, the mean was 8.2 with a range of 6 to 10, and 8.3% with a score below 7.

Few side effects were observed. Seven patients in the study series (6.5%) and one in the control group (8.3%) developed a transient irregular pulse. One patient in the study group developed bradycardia (56 bpm at 60 min). Seven patients in the study group complained of being cold upon awakening; one developed nausea; another cried; none experienced excessive salivation.

DISCUSSION

Scopolamine, classified as an anticholinergic agent, competes with acetylcholine at the motor endplate and in postganglionic neural synapses. Anticholinesterases such as physostigmine inhibit the hydrolysis of acetylcholine by cholinesterase, permitting prolonged action and buildup of acetylcholine at these synapses.

Bernards[2] has shown that physostigmine will arouse patients sedated with certain phenothiazines such as chlorpromazine and thioridazine, although the mechanism of action is not clear. Thus, it is possible that the physostigmine not only reversed the scopolamine but also the propiomazine in our patients.

Physostigmine is totally eliminated from the body within 2 hours.[9,12] Unlike its analogue, neostigmine, it passes the blood-brain

barrier and readily affects central nervous tissue synapses.[13] Hence, the patient, who has been completely unconscious during her labor and delivery, suddenly awakens when given this drug, looks around, and converses.

Although our total meperidine and scopolamine dosage was not as high as reported by some authors,[14,15] we have found it adequate for satisfactory analgesia and amnesia. Only occasionally have we seen untoward side effects. The mean dose of 2 mg of physostigmine was similar to that given in other studies. Our largest dose was 3.6 mg. Smiler's group[9] gave 4 mg IV, while Goldner[16] gave 10 mg IM without untoward results.

Anticholinesterases can cause bradycardia through muscarinic effects.[13] Only 1 patient experienced this effect in our series. In previous studies of physostigmine reversal of anticholinergic agents, only 1 other case of bradycardia has been reported.[11] Atropine, which in a dose of one-half that of the administered physostigmine will reverse any side effect of physostigmine,[10] was available if significant decrease in maternal pulse occurred but was never needed.

Greene[7] reported transient ectopic heartbeats secondary to physostigmine administration in 1/31 patients. The irregular pulse in 7 of our patients was also transient and was not dose related. These phenomena possibly reflect the fact that anticholinesterase drugs can increase the conduction time in the heart. They can also cause a prolonged P-R interval, inversion of P waves, increased amplitude of the QRS complex, and increased height of T waves.[13] We did not consider the cardiovascular changes in our study to be clinically significant.

That 7 patients in the study series complained of being cold upon awakening was of interest. Forrer and Miller[4] noted a drop in temperature in some of their patients given physostigmine. It is known that scopolamine will cause a rise in body temperature, especially after high doses.[13] Goldner[16] demonstrated an apparent reversal of high-dose scopolamine hyperthermia with physostigmine. Although excessive salivation was reported in one-half of Holzgrafe's series,[11] none of our patients experienced this problem.

ACKNOWLEDGMENT

The authors express their appreciation to the Division of Biometry, University of Arkansas for Medical Sciences, for statistical evaluations, Mrs. Renee Robbins, BS, for her help in organizing the data, and to Mrs. Carol Bridges, RN, and her nursing staff for their help in collecting the data.

REFERENCES

1. Sherman RL, Cabell BB, Clark RB: Sparine-Demerol-scopolamine analgesia for labor and delivery. J Arkansas Med Soc 67:293-296, 1971

2. Bernards W: Case history number 74: Reversal of phenothiazine-induced coma with physostigmine. Anesth & Analg 52:938-941, 1973

3. Duvoisin RC, Katz R: Reversal of central anticholinergic syndrome in man by physostigmine. JAMA 206:1963-1965, 1968

4. Forrer GR, Miller JJ: Atropine coma: a somatic therapy in psychiatry. Am J Psychiat 115: 455-458, 1958

5. Crowell EB, Ketchum JS: The treatment of scopolamine-induced delirium with physostigmine. Clin Pharmacol Ther 8:409-414, 1967

6. Young SE, Ruiz RS, Falletta J: Reversal of systemic toxic effects of scopolamine with physostigmine salicylate. Am J Ophthalmol 72:1136-1138, 1971

7. Greene LT: Physostigmine treatment of anticholinergic-drug depression in postoperative patients. Anesth & Analg 50:222-226, 1971

8. Ullman KC, Groh RH: Identification and treatment of acute psychotic states secondary to the usage of over-the-counter sleeping preparations. Am J Psychiat 128:1244-1248, 1972

9. Smiler BG, Bartholomew EG, Sivak BJ, et al: Physostigmine reversal of scopolamine delirium in obstetric patients. Am J Obstet Gynecol 116: 326-329, 1973

10. Rumack BH: Anticholinergic poisoning: treatment with physostigmine. Pediatrics 52:449-451, 1973

11. Holzgrafe RE, Vondrell JJ, Mintz SM: Reversal of postoperative reactions to scopolamine with physostigmine. Anesth & Analg 52:921-925, 1973

12. Weiss S: Persistence of action of physostigmine and the atropine-physostigmine antagonism in animals and in man. J Pharmacol Exp Ther 27: 181-188, 1926

13. Koelle GB: Anticholinesterase agents, The Pharmacological Basis of Therapeutics. Fifth edition. Edited by AS Goodman, A Gilman. New York, The Macmillan Company, 1975, chapter 22

14. Clark RB, Cooper JO, Stephens SR, et al: Neonatal acid-base studies. II: Effect of a heavy medication-narcotic antagonist regimen for labor and delivery. Obstet Gynecol 33:30-34, 1969

15. Rodgers CD, Wickard CP, McCaskill MR: Labor and delivery without terminal anesthesia. A report on the use of chlorpromazine. Obstet Gynecol 17:92-95, 1961

16. Goldner RD: Scopolamine sleep treatment in private practice. Int J Neuropsychiat 3:234-247, 1967

Respiratory Distress With Left Aortic Arch, Right Descending Aorta, And Right Ligamentum Arteriosum: A Case Report

S. S. MOORTHY, MB, BS, MD*
EDMUND A. FRANKEN, MD†
ALVIN M. LoSASSO, MD‡
HAROLD KING, MD§
Indianapolis, Indiana‖

A 7-year-old girl manifested the rare anomaly of a ventricular septal defect (VSD) with left aortic arch, right descending aorta, and right ligamentum arteriosum. After open-heart surgery to correct the VSD, symptoms of tracheal obstruction on spontaneous breathing developed, due to tracheal compression by the right ligamentum arteriosum. The compressed segment of the trachea was found to be thin and unstable following division of the ligamentum. Positive-pressure breathing and continuous positive airway pressure breathing effectively splinted the patient's airway during the postoperative period, with recovery of the patient.

VASCULAR rings associated with anomalies of the great vessels in the superior mediastinum are common and may assume many forms.[1-3] In view of their close proximity to the trachea and esophagus, vascular rings can produce symptoms by compression of these vital passages. The presence of a left-sided aortic arch with a right-sided descending aorta and a right ligamentum arteriosum is uncommon. Murthy's group[4] reported a case and reviewed 13 previously recorded cases.

The present report describes a case of a 7-year-old girl who had a ventricular septal defect (VSD), left aortic arch, right descending aorta, and right ligamentum arteriosum. The ligamentum produced respiratory distress by compression of the trachea and tracheomalacia.

CASE REPORT

The patient, admitted for repair of a large VSD, had undergone pulmonary artery banding with good results at 3 months of age. She had repeated respiratory tract infections with occasional croup, considered of infectious origin, and had been treated with digoxin for recurrent congestive heart failure. There was no history of dysphagia or chronic respiratory distress.

The patient was underdeveloped, with normal vital signs. While the cardiovascular system revealed signs of VSD, other systems showed no abnormalities.

The PA chest roentgenogram showed cardiomegaly and increased pulmonary vasculature. The aortic knob was not visualized

*Assistant Professor, Department of Anesthesiology.
†Associate Professor, Department of Radiology.
‡Associate Professor, Department of Anesthesiology.
§Professor, Department of Surgery; Director, Section of Thoracic and Cardiovascular Surgery.
‖Departments of Anesthesiology, Roentgenology, and Thoracic Surgery, Indiana University School of Medicine, Indianapolis, Indiana 46202.

Paper received: 9/26/75
Accepted for publication: 11/13/75

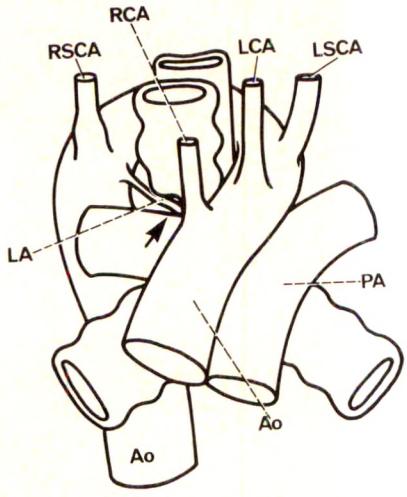


FIG 1. Diagram of the vascular anomaly. Arrow indicates ligamentum arteriosum with compression of trachea. AO = aorta; PA = pulmonary artery; LSCA = left subclavian artery; LCA = left common carotid artery; RCA = right common carotid artery; RSCA = right subclavian artery; LA = ligamentum arteriosum.

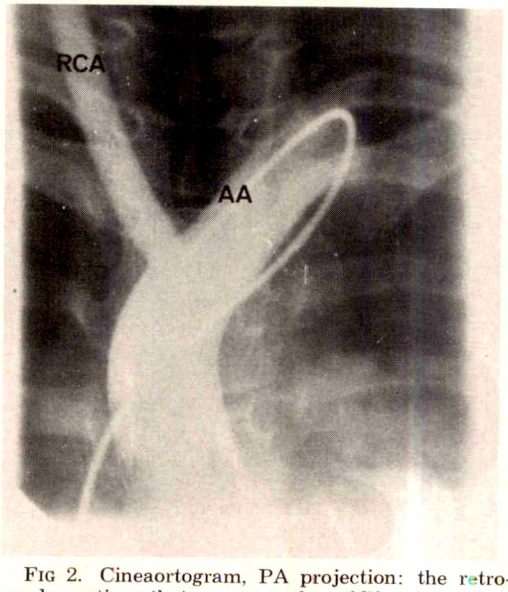


FIG 2. Cineaortogram, PA projection: the retrograde aortic catheter crosses the midline from right to left at the level of the 5th dorsal vertebra and enters the ascending aorta from the left. This initial cine frame after supravalvar injection of contrast material opacifies the ascending aorta (AA). The first brachiocephalic vessel is the right common carotid artery (RCA).

but a right descending aorta could be identified. On the lateral roentgenogram, posterior indentation of the trachea superior to the carina was noted.

Aortography in PA and lateral projections demonstrated a left aortic arch with right descending aorta (figs 1-4). The operative

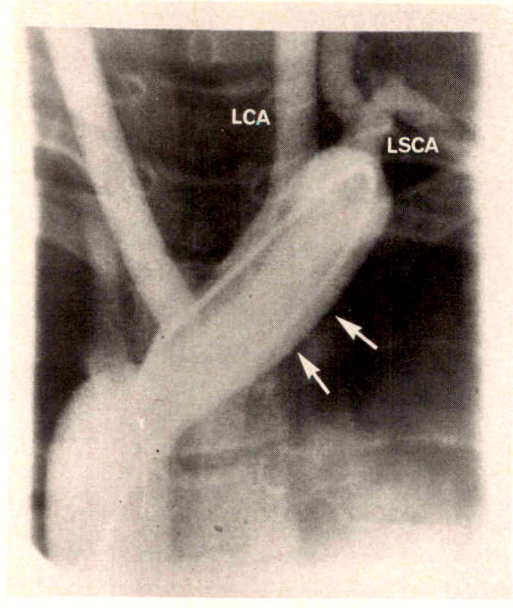


FIG 3. A later frame from the same injection as figure 2, showing the left common carotid (LCA) and left subclavian (LSCA) arteries originating from the aortic arch. The aortic arch is above the clavicle, and the distal left arch (arrows) extends inferiorly, to the right, and posteriorly (noted on the lateral cine, not illustrated), and joins the right descending aorta at the origin of the right subclavian artery.

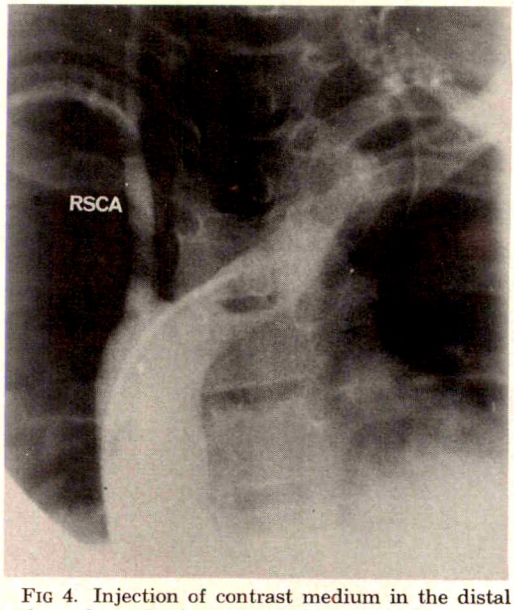


FIG 4. Injection of contrast medium in the distal arch confirms the junction of the arch and descending aorta on the right at the origin of the right subclavian artery (RSCA).

and anesthetic procedures involved meperidine, dimethyltubocurarine, N_2O-O_2, and cardiopulmonary bypass. The pulmonary

artery banding and the VSD were repaired. The origin of the aorta and pulmonary trunk were noted to be normal but the descending aorta was found to be on the right side.

Postoperatively, the patient was placed on an Engström volume ventilator with controlled ventilation. With the administration of 35% O_2, blood gases were Pao_2 118 torr, $Paco_2$ 35.7 torr, pH 7.395, and base excess −1. On the morning of the 2nd postoperative day, the patient was tried off the ventilator, breathing 40% O_2 via T-tube. Within 2 minutes, she became restless, cyanotic, and showed signs of upper-airway obstruction. The endotracheal tube was patent and the patient was returned to the ventilator.

She was again tried off the ventilator several times in the next 24 hours without success, each time showing symptoms of upper-airway obstruction. Endoscopy under general anesthesia, using halothane-O_2 and a ventilating bronchoscope, revealed a 1-cm extrinsic, nonpulsatile compression of the trachea of the right and posterior side just above the carina, indicating compression by a vascular ring.

On the 4th postoperative day, operation was performed through a right thoracotomy using fluroxene-N_2O-O_2. A ligamentum arteriosum, 0.5 cm in diameter, was found to the right of the trachea, extending from the right pulmonary artery to the arch of the aorta, with the right recurrent laryngeal nerve around it. After division of the ligament, the trachea was found to be thin and easily collapsible at the site of compression (tracheomalacia) (fig 1).

After operation, repeated attempts to wean the patient from the ventilator failed, the patient again manifesting signs and symptoms of upper-respiratory obstruction. An elective tracheostomy was done on the 8th postoperative day. On the 10th postoperative day, she could be maintained for a few minutes off the ventilator with the use of continuous positive airway pressure (CPAP). Progressively, the periods on CPAP were increased, with final weaning from the ventilator. The patient could then be gradually weaned off the CPAP by the 15th postoperative day. Throughout the postoperative course, the O_2 exchange was satisfactory.

DISCUSSION

The association of a left aortic arch with a right descending aorta is an uncommon anomaly, 2 cases associated with tetralogy of Fallot and 1 case not associated with cardiac abnormality[6] having been reported in 1948. Klinkhamer[7] reviewed 8 cases in 1969, and in addition reported 1 case of his own, noting symptoms of tracheoesophageal compression in 3 of the 8 cases. While the course of the transverse segment of the arch of the aorta may be retroesophageal or pretracheal, the former is more common.[7]

The vascular ring is formed on the left by the aortic arch, posteriorly by the transverse portion of the aortic arch, to the right by the ligamentum arteriosum or patent ductus, and anteriorly by the pulmonary arteries.[6] Symptoms due to vascular ring are usually manifest in the newborn or the elderly.[6]

In this anomaly, the ascending aorta is elongated with the aortic knob usually in the neck. The first branch is a right common carotid artery, followed by a left common carotid artery and left subclavian artery. Beyond the aortic knob, the aorta swings posteriorly and to the right behind the esophagus to join a right descending aorta. At this junction a right subclavian artery usually arises with a bulbous origin.

Even though our patient showed radiologic evidence of tracheal compression preoperatively, there were no symptoms indicative of obstruction. She became symptomatic following operation.

Ductus arteriosus or ligamentum arteriosum commonly lies on the same side of the body as the upper portion of the descending aorta.[6] In the present case, bronchoscopy aided in the localization of the site of compression. Surgical correction of the compressing lesion has been helpful to alleviate the symptoms and has been recommended by Gross[1] and by Neuhauser.[3] Tracheomalacia in a patient suffering from infectious polyneuritis with inspiratory obstruction, whose symptoms improved with temporary reinsertion of an uncuffed cannula, has been reported.[8] Our patient demonstrated tracheal weakness just above the carina, and introduction of an endotracheal tube was prevented by the likelihood of carinal stimulation and endobronchial intubation.

Preoperative evaluation of the trachea and esophagus by radiology is important in all cases with vascular anomalies in the mediastinum. Ligaments, vessels, and fibrous bands or sheaths accompanying the

vessels and ligaments produce an obstruction of the trachea and esophagus. Positive-pressure breathing and CPAP appear beneficial for treating the respiratory distress associated with airway obstruction or tracheomalacia in these cases.

ACKNOWLEDGMENT

We thank Dr. Donald A. Girod, Professor and Director of Pediatric Cardiology, Indiana University Medical Center, for his cooperation, and Miss Linda Hicks for her secretarial assistance.

REFERENCES

1. Gross RE: Arterial malformations which cause compression of the trachea or esophagus. Circulation 11:124-134, 1955

2. Blake HA, Manion WC: Thoracic arch anomalies. Circulation 26:251-265, 1962

3. Neuhauser EBD: Tracheo-esophageal constriction produced by right aortic arch and left ligamentum arteriosum. Am J Roentgenol 62:493-499, 1949

4. Murthy K, Mattioli L, Diehl AM, et al: Vascular ring due to left aortic arch, right descending aorta and right patent ductus arteriosus. J Pediatr Surg 5:550-554, 1970

5. Paul RN: A new anomaly of the aorta. Left aortic arch with right descending aorta. J Pediatr 32:19-29, 1948

6. Edwards JE: Retro-esophageal segments of the left aortic arch, right ligamentum arteriosum and right descending aorta causing a congenital vascular ring about trachea and esophagus. Mayo Clin Proc 23:108-116, 1948

7. Klinkhamer AC: Esophagography in Anomalies of the Aortic Arch System. Baltimore, The Williams & Wilkins Company, 1969, pp 78-82

8. Bendixen HH, Egbert LD, Hedley-Whyte J, et al: Respiratory Care. St. Louis, The CV Mosby Company, 1965, pp 118-119

Influence of Pancuronium or d-Tubocurarine on Circulatory Responses During Thiamylal-N_2O-Halothane Anesthesia

ROBERT K. STOELTING, MD*

Circulatory responses after thiamylal (4 mg/kg) and pancuronium (0.08 mg/kg, 20 patients) or d-tubocurarine (dTc, 0.5 mg/kg, 20 patients) followed by tracheal intubation and nitrous oxide-halothane administration were measured. Three minutes after thiamylal, the mean arterial pressure (MAP) and cardiac index (CI) decreased significantly only in patients receiving dTc. Heart rate (HR) was increased 12 bpm in both groups. The magnitude of reduction in MAP and CI was similar and the HR was not greatly different between groups after 5 minutes of N_2O-halothane administration.

MAP and CI were better maintained following thiamylal in patients receiving pancuronium as compared with dTc. However, circulatory responses during early anesthetic maintenance were not influenced by the choice of neuromuscular blocker.

CIRCULATORY changes may result from drugs used for anesthetic induction and maintenance and from the stimulation of tracheal intubation. In addition, competitive neuromuscular blocking agents may produce hemodynamic alterations. For example, in one report,[1] pancuronium (0.08 mg/kg) increased mean arterial pressure (MAP), heart rate (HR), and cardiac output following rapid IV administration during N_2O-halothane anesthesia, while 0.4 mg/kg of d-tubocurarine (dTc) slightly increased HR and decreased blood pressure (BP), cardiac output, and systemic vascular resistance (SVR). In view of the different circulatory responses produced by these two drugs, we speculated that the direction and/or magnitude of circulatory changes occurring during anesthetic induction, tracheal intubation, and anesthetic maintenance might be influenced by the choice of neuromuscular blocker.

This study compares circulatory responses after thiamylal anesthetic induction, tracheal intubation, and subsequent anesthetic maintenance with N_2O-halothane in the presence of either pancuronium or dTc paralysis.

METHODS

Forty adult patients without known heart disease and requiring elective operations were studied. All had received morphine (8 to 12 mg) and atropine (0.4 mg) IM as preanesthetic medication 60 to 90 minutes before operation. On their arrival in the operating room, a radial artery catheter was inserted percutaneously and attached to a strain gauge and recorder for continuous recording of MAP. Lead 2 of the ECG was recorded continuously. After breathing O_2 by mask for 3 minutes, awake MAP and cardiac output (dye-dilution method with indocyanine green dye) were measured. Cardiac index (CI), stroke volume index (SVI), and SVR were calculated, while HR was measured from a 15-second portion of the ECG.

Twenty patients received pancuronium (0.1 mg/kg) as a bolus IV and the other 20 patients dTc (0.5 mg/kg). Thirty seconds after neuromuscular blocker injection, anesthetic induction was accomplished in

*Professor of Anesthesiology/Pharmacology, Indiana University School of Medicine, Indianapolis, Indiana 46202.

Paper received: 11/6/75
Accepted for publication: 11/19/75

all patients by the rapid IV administration of thiamylal (4 mg/kg). Ventilation was manually controlled by mask with O_2 within 15 seconds of thiamylal injection.

Cardiac output was again measured 1 and 3 minutes after thiamylal administration. After the 3-minute measurement, the response to 3 seconds of continuous ulnar nerve stimulation (tetanus) was visually noted utilizing a peripheral nerve stimulator (Block-Aid® Monitor, 50 Hz). Direct laryngoscopy and orotracheal intubation was then accomplished. Laryngotracheal lidocaine (2 mg/kg) was administered just before placement of the tube in the trachea. Immediately following endotracheal intubation, ventilation was mechanically controlled with 60% N_2O-O_2 (3:2) and about 1% delivered halothane. All measurements were repeated after 5 minutes of anesthetic maintenance with these drugs. Arterial blood for blood-gas analysis and blood-halothane levels were also obtained at this time.

Data within and between the 2 groups were compared by Student's *t*-test, with $p<0.05$ considered statistically significant. This study was approved by the Indiana University School of Medicine Clinical Research Committee.

RESULTS

Patient data and drug dosages are summarized in table 1 and all other measurements are detailed in table 2. Awake MAP was not changed from control measurements

TABLE 1

Patient Data and Mean (± SE) Drug Dosages

	Pancuronium	dTc
Number of patients	20	20
Age, years	40 ± 3	42 ± 4
Weight, kg	66 ± 3	70 ± 3
Neuromuscular blocker, mg	6.6 ± 0.3	35 ± 2

TABLE 2

Measurements Awake and After Drug Administration (Mean ± SE)

	Awake	30 seconds after neuromuscular blocker injection	Minutes after thiamylal injection		After 5 minutes N_2O-halothane administration
			1	3	
MAP, torr					
Pancuronium	99 ± 3	103 ± 3	93 ± 3	93 ± 4	86 ± 3*
dTc	100 ± 3	98 ± 3	76 ± 3*†	82 ± 3*†	81 ± 4*
HR, bpm					
Pancuronium	78 ± 4	90 ± 4*	90 ± 3*	86 ± 3	85 ± 3
dTc	78 ± 5	82 ± 6	90 ± 4	92 ± 4	82 ± 3
CI, L/min/m²					
Pancuronium	3.2 ± 0.1		3.0 ± 0.2	3.4 ± 0.2	2.6 ± 0.2*
dTc	3.3 ± 0.2		2.9 ± 0.2	2.7 ± 0.2*†	2.2 ± 0.2*
SVI, ml/beat/m²					
Pancuronium	41 ± 4		33 ± 4	39 ± 2	31 ± 2*
dTc	42 ± 3		32 ± 2*	29 ± 2*	28 ± 2*
SVR, torr/L/min/m²					
Pancuronium	31 ± 2		31 ± 3	27 ± 3	33 ± 2
dTc	30 ± 4		26 ± 3	30 ± 4	37 ± 4
Arterial halothane, mg/100 ml					
Pancuronium					6.2 ± 0.6
dTc					6.6 ± 0.4
Pa_{O_2}, torr					
Pancuronium					174 ± 9
dTc					189 ± 11
Pa_{CO_2}, torr					
Pancuronium					31 ± 1
dTc					31 ± 1

*$p<0.05$ compared with awake measurement.

†$p<0.05$ dTc compared with pancuronium measurement at same time.

30 seconds after either pancuronium or dTc, but HR was increased after pancuronium ($p<0.05$). MAP was decreased an average of 24 torr ($p<0.05$) and 18 torr ($p<0.05$) 1 and 3 minutes, respectively, after thiamylal administration to patients receiving dTc. In contrast, MAP was not significantly decreased at these times following thiamylal administration to patients given pancuronium. Three minutes following thiamylal administration, CI and SVI were decreased ($p<0.05$) in patients receiving dTc but not in those given pancuronium.

Tracheal intubation between 3 and 4 minutes following thiamylal administration was accomplished in all patients but intubating conditions were considered better in patients receiving pancuronium. Of 20 patients receiving dTc, 17 coughed with placement of the tracheal tube, while only 2/20 coughed with pancuronium. The tetanus response to ulnar nerve stimulation was visually judged to be depressed at least 75% in 5/20 patients receiving dTc and 14/20 receiving pancuronium. Despite similar durations of direct laryngoscopy, the MAP achieved in response to this stimulation was greater in patients receiving pancuronium than in those given dTc (140 versus 115 torr, $p<0.05$).

Compared with awake measurements, MAP, CI, and SVI were decreased ($p<0.05$) in both groups after 5 minutes of controlled ventilation with 60% N_2O and 1% halothane. Furthermore, MAP, HR, CI, SVI, and SVR at this time were not significantly different between groups. The arterial halothane concentrations and blood gases were similar in both groups. The halothane concentrations were equivalent to 0.3 to 0.4 vol/100 ml, assuming a blood/gas partition coefficient equal to 2.4.

DISCUSSION

Pancuronium (0.08 mg/kg) has been demonstrated to increase MAP, HR and cardiac output following rapid intravenous administration during nitrous oxide-halothane anesthesia while dTc (0.4 mg/kg) slightly increased HR and reduced blood pressure, cardiac output and SVR.[1] Conceivably, large doses of dTc combined with thiamylal for anesthetic induction could have an additive effect with barbiturate-produced circulatory effects, resulting in undesirable degrees of hypotension. In contrast, the circulatory effects of pancuronium might attenuate the circulatory response to barbiturate anesthetic induction. Indeed, this study demonstrated that MAP and cardiac output did not change significantly in the first 3 minutes after thiamylal administration to patients receiving pancuronium, as contrasted with significant reductions in these parameters in patients given dTc. HR increased by similar amounts regardless of the neuromuscular blocker chosen, although the increase occurred sooner and was statistically significant only in patients receiving pancuronium.

Intubating conditions at the dose and time interval chosen in our study were better with pancuronium than with dTc. Other workers[2,3] have also reported more acceptable intubating conditions with pancuronium than with dTc. Perhaps a larger dose of dTc would have provided more acceptable conditions with this drug, although Bennett and associates,[4] using 0.12 mg/kg pancuronium or 0.6 mg/kg dTc, found no significant difference between the drugs for tracheal intubation.

Despite similar durations of direct laryngoscopy the maximal MAP attained in response to this stimulation was significantly greater in patients receiving pancuronium. Considering the MAP at the start of laryngoscopy the absolute increase in blood pressure was 33 torr in patients receiving dTc and 47 torr in patients given pancuronium. This decreased pressor response to laryngoscopy and tracheal intubation might reflect dTc-produced autonomic ganglion blockade which would be less with pancuronium.[5]

Controlled ventilation with N_2O-halothane may be associated with circulatory depression. We speculated that circulatory changes resulting from pancuronium might attenuate subsequent responses during anesthetic maintenance, while dTc might produce an additive depressant effect, especially on blood pressure. However, MAP, CI, and SVI were significantly reduced from awake measurements after 5 minutes of similar anesthetic maintenance in both groups. Furthermore, the MAP, HR, CI, SVI, and SVR were not significantly different between groups, although CI was nearer awake measurements in patients receiving pancuronium.

We conclude that MAP and CI are better maintained following thiamylal anesthetic induction in patients receiving prior pancuronium as compared with dTc. Intubating conditions at the drug dosages and time intervals chosen in this study were better

with pancuronium than dTc. Blood pressure increased more in response to laryngoscopy and tracheal intubation in patients receiving pancuronium. Circulatory changes after controlled ventilation for 5 minutes with N_2O-halothane did not seem to be altered by the presence of pancuronium or dTc paralysis.

REFERENCES

1. Stoelting RK: The hemodynamic effects of pancuronium and d-tubocurarine in anesthetized patients. Anesthesiology 36:612-615, 1972

2. McDowell SA, Clark RS: A cilinical comparison of pancuronium with d-tubocurarine. Anaesthesia 24:581-590, 1969

3. Catton DV, Browne RA: A double blind comparison of pancuronium and d-tubocurarine for endotracheal intubation. Can Anaesth Soc J 19: 305-308, 1972

4. Bennett EJ, Gieszl GS, Dalal FY: Pancuronium bromide: a double-blind comparison with d-tubocurarine for intubation in adults. Anesth & Analg 52:195-197, 1973

5. Buckett WR, Majoribanks CEB, Marwick FA, et al: The pharmacology of pancuronium bromide (ORG NA97), a new potent steroidal neuromuscular blocking agent. Br J Pharmacol 32:671-682, 1968

PROPRANOLOL WITHDRAWAL. The authors measured the persistence of propranolol in plasma and atrial tissue following drug withdrawal, tested for residual beta-adrenergic blockade with isoproterenol and determined the plasma disappearance rate following a single intravenous dose to treat intraoperative dysrhythmias. In 34 patients withdrawn from chronic propranolol therapy 18-48 hours preoperatively, propranolol was detected in the plasma of 9 and in atrial tissue of 5. Following bolus, intravenous isoproterenol, 3 μg, heart rate increased greater than 20 beats/min in all patients withdrawn from propranolol at least 18 hours preoperatively as well as patients never having received propranolol. The highest plasma propranolol was 23 ng/ml in a patient taking 300 mg/day orally. These data suggest that concern about persisting beta blockade after oral propranolol withdrawal need arise only in patients taking doses greater than 300 mg. Furthermore, any questions concerning persisting blockade could be resolved by administering 3 μg isoproterenol and observing the heart rate response. Propranolol was not detectable in the plasma or atrial tissue 5 minutes after a single intravenous 0.5 mg injection. The authors conclude that early preoperative withdrawal (greater than 24 hours) of propranolol in patients with coronary artery disease may be more hazardous than beneficial. *(Romagnoli A, Keats AS: Plasma and atrial propranolol after preoperative withdrawal. Cir 52:1123-1127, 1975)*

Spinal Anesthesia: Bupivacaine Versus Tetracaine

A. EUGENE PFLUG, MD*
GEORDIS M. AASHEIM, MD†
HAROLD A. BECK, BS‡
Seattle, Washington§

The clinical effects of equal hyperbaric doses of bupivacaine HCl and tetracaine HCl were studied and compared in 99 adult men undergoing spinal anesthesia for similar surgical procedures. The spinal anesthetic agents were used in random order in various dosages. Comparisons were made of (1) amount of anesthetic agent used, (2) elapsed time for onset of analgesia, (3) elapsed time for obtaining maximum anesthesia, (4) cephalad dermatome level of anesthesia, (5) incidence of motor blockade, and (6) duration of anesthesia. Results with the 2 drugs in equal dose, volume, and specific gravity were almost identical. However, tetracaine provided a motor block in a significantly greater number of patients than did bupivacaine (100 versus 42%, $p<0.001$) when both drugs were used at the 9.75-mg dose level.

ONE OF the objectives of research involving local anesthetics for regional anesthesia is the prolongation of the duration of sensory anesthesia without an increase in adverse effects or toxicity. Bupivacaine (Marcaine®) extends the duration of sensory anesthesia without increasing toxicity when used for peridural or peripheral nerve blocks.[1] Spinal anesthesia with bupivacaine is reportedly efficacious and safe,[2-4] and may be of longer duration than subarachnoid block with tetracaine (Pontocaine®).

The objective of our study was to compare the observed clinical properties of bupivacaine spinal anesthesia with those of a conventional tetracaine spinal, using equal hyperbaric doses for similar surgical conditions.

METHODS

Ninety-nine adult men were studied for 24 hours after spinal anesthesia for elective surgery. Prior informed consent was obtained from each. Patients were accepted for study if they were without infection of tissues in the lumbar area, evidence of hypovolemia, uncontrolled systemic disease, or history of cerebrospinal-system disease.

Ninety-nine numbered vials‖ were arranged in random order, each containing 15 mg of either bupivacaine or tetracaine in 5 percent glucose solution within a total volume of 2 ml. The resultant solutions contained 7.5 mg/ml of local anesthetic agent of the same volume and specific gravity, which allowed direct comparison of the drugs. Dosage was based on age, weight, height, physical condition, and anesthetic and surgical procedures, these factors being standardized in grouping, so far as possible.

The more anxious patients (11 receiving

‖Sterling Winthrop Laboratories.

*Assistant Professor.
†Assistant Professor.
‡Medical Student.
§Department of Anesthesiology and Anesthesia Research Center, University of Washington School of Medicine, Seattle, Washington 98195.

This study was supported in part by USPHS Grant GM 15991-05 from the National Institute of General Medical Sciences, Grant RR-133 from the General Clinical Research Center Program of the Division of Research Resources, National Institutes of Health, and a Grant from Sterling-Winthrop Research Institute, Division of Sterling Drug Incorporated, Rensselaer, New York.

Paper received: 11/3/75
Accepted for publication: 12/4/75

tetracaine, 7 receiving bupivacaine) received preoperative medication consisting of 5 or 10 mg of IM diazepam, depending on size and age. All patients had an IV infusion started with an 18 or 16-gauge plastic catheter, blood pressure cuff applied to an arm, and leads connected to a cardioscope monitor. Standard lumbar paramedian spinal anesthesia was administered with a 22-gauge needle while the patient was in the left lateral recumbent position. Mephentermine 1 ml (30 mg) was injected through the skin wheal used for insertion of the spinal needle into the perispinal muscles immediately following injection of the local anesthetic agent into the subarachnoid space. An IV infusion of 500 to 700 ml of lactated Ringer's solution was completed prior to injection of the spinal anesthetic agent. The mephentermine and IV fluids were used to help prevent the vascular hypotension which can be associated with spinal anesthesia. The operating table was flexed (patient's legs elevated, back horizontal) to help prevent backache, which often follows the prolonged supine position, and to promote venous return from the legs. The entire table was further manipulated to obtain the desired dermatome level of analgesia.

Spinal anesthesia was supplemented by intermittent IV diazepam (5 to 10 mg) or thiamylal (50 to 75 mg) for sedation after maximal regional anesthesia had been obtained (10 patients in the bupivacaine group, 16 patients in the tetracaine group). Nasal O_2 was administered during the operative procedure when indicated by age or chronic disease. Measured blood loss was replaced intraoperatively in addition to maintenance fluids to help prevent vascular hypovolemia.

The following observations were made: (1) amount of anesthetic agent used, (2) time anesthetic agent was injected, (3) time of onset of analgesia, (4) time maximum surgical anesthesia was obtained, (5) presence or lack of motor function blockade of the legs, (6) highest dermatome level of maximum anesthesia, (7) time of onset anesthesia regression, and (8) time anesthesia regression was complete (table). Blood pressure, pulse, and respiration were monitored at the following times: preoperatively on the ward, preoperatively in the operating room, intraoperatively at 5-minute intervals, and postoperatively at 10-minute intervals until sensory sensation had fully returned. Drugs and amounts used to supplement spinal anesthesia were recorded intraoperatively and quality of surgical anesthesia assessed postoperatively.

Onset of analgesia was defined as loss of sensory sensation to pinprick in the suprapubic area, and surgical anesthesia as loss of sensory sensation to skin-fold clamping with an Allis forceps to the first rachet. Motor blockade was arbitrarily defined as the inability to straight-leg raise the heels off the operating table. Maximum surgical anesthesia (Allis forceps) was equated with the time cephalad dermatome progression of anesthesia ceased, onset of regression as the time the dermatome level of anesthesia started moving in a caudad direction, and complete regression as the time sensation returned in the suprapubic area (Allis forceps). Anesthesia was rated as satisfactory when the patient did not complain of pain during the operation or the surgeon comment negatively about anesthetic conditions.

The key to the identity of all numbered vials was opened at the completion of the study for analysis of results. Statistical significance was determined by Student's *t*-test for paired data.

RESULTS (table)

No significant difference was noted between mean values for the tetracaine and bupivacaine groups for age and height. However, the mean kilogram weight of the patients receiving the 15 mg tetracaine anesthesia was significantly greater than the corresponding value for the bupivacaine group (84.5 versus 71.5 kg, $p<0.01$), and the mean mg/kg local anesthetic dose received by the patients in the 15 mg bupivacaine group was significantly greater than the corresponding amount for the tetracaine group (2.2 versus 1.8 mg/kg, $p<0.01$).

These differences did not, however, significantly prolong the duration of the 15 mg bupivacaine spinal anesthesia compared with 15 mg of tetracaine, results obtained with the 2 drugs in equal dose, volume, and specific gravity being almost identical. No significant difference was found between the mean values for time of onset, time of maximal anesthesia, dermatome level of anesthesia, or duration of spinal anesthesia produced by equal amounts of bupivacaine and tetracaine.

The only difference noted in comparing the 2 drugs was in the incidence of motor function blockade. Tetracaine provided a motor block in a significantly greater number of patients than did bupivacaine (100 versus 42%, $p<0.001$) when both drugs were used at the 9.75 mg dose level. Both

TABLE

Values for Characteristics of the Patients Studied Plus Clinical Properties of the Spinal Anesthesia Provided by Bupivacaine (B) and Tetracaine (T) at Various Dose Levels (Mean ± SE)

Group	Low dose		Medium dose		High dose		Combined	
	T	B	T	B	T	B	T	B
N	13	13	12	12	19	21	50	49
Dose, mg	7.5	7.5	9.75	9.75	15	15	10.9	11.1
Dose, mg/kg	0.96	0.98	1.5	1.4	1.8	2.2*	1.5	1.6
SE	±0.05	±0.04	±0.06	±0.12	±0.08	±0.08	±0.07	±0.09
Age, yr	57	64	58	63	55	66	59	65
SE	±5.2	±4.1	±5.7	±4.0	±4.3	±3.6	±2.7	±2.1
Weight, kg	82	78	67	73	85*	72	76	73
SE	±4.8	±3.2	±2.6	±5.3	±3.9	±2.7	±2.5	±2.0
Height, cm	177	176	175	180	180	175	177	176
SE	±1.9	±1.6	±2.9	±1.8	±1.5	±1.6	±1.1	±1.0
Onset, min†	3.2	4.2	2.9	3.7	3.2	2.6	3.0	3.3
SE	±0.5	±0.6	±0.2	±0.5	±0.3	±0.2	±0.2	±0.3
Max, min‡	15.2	12.9	12.9	12.8	13.1	12.8	13.7	12.7
SE	±1.4	±0.8	±1.1	±1.1	±1.0	±1.1	±0.6	±0.6
Level, thoracic§	9	8	8	9	7	7	8	8
SE	±0.4	±0.7	±0.6	±0.5	±0.4	±0.4	±0.3	±0.3
Percent motor‖	62	46	100	42**	90	71	84	57
SE	±0.1	±0.1	±0.0	±0.2	±0.1	±0.1	±0.1	±0.1
Regression††	72	74	84	78	110	113	88	90
Start, min	±6	±8	±7	±7	±6	±8	±4	±5
Regression‡‡	142	121	164	143	189	198	163	159
Complete, min	±14	±13	±17	±11	±8	±11	±7	±8

*$p<0.01$.

†Onset = time of onset suprapubic analgesia.

‡Max = time cephalad dermatome progression of anesthesia ceased.

§Level = highest dermatome level of anesthesia.

‖Percent motor = percent of patients with leg paralysis.

**$p<0.001$.

††Regression start = elapsed time from injection of anesthetic agent to time the dermatome level of anesthesia started moving in a caudad direction.

‡‡Regression complete = elapsed time from injection of anesthetic agent to time sensation returned to suprapubic area.

bupivacaine and tetracaine provided satisfactory spinal anesthesia for all the surgical procedures studied. Tetracaine was used for spinal anesthesia for the following operations: urology (other than intraperitoneal) 39, perineum 4, orthopedic (hips and legs) 4, inguinal hernia 3. Spinal anesthesia with bupivacaine was used for urology 37, perineum 2, orthopedic 8, and inguinal hernia 2. Hypotension (20% decrease in systolic blood pressure from preoperative level) was noted in 3/99 anesthetic procedures, all in the bupivacaine group. These episodes of hypotension were easily reversed by the use of increased IV fluids and IV ephedrine. One patient developed a headache after tetracaine, which resolved with conservative treatment.

DISCUSSION

Reported results of bupivacaine peridural anesthesia indicate a longer duration of block than a similar block with tetracaine.[1] Bupivacaine might be expected to also prolong duration of spinal anesthesia, but such prolongation was not revealed by our study (table) when the 2 drugs were compared on

a milligram-to-milligram basis. However, the duration of spinal anesthesia was increased 33 and 63% by doubling dosage of both agents (7.5 versus 15 mg), without changing the time of onset, time of maximum anesthesia, or thoracic dermatome level of anesthesia (table).

In 321 cases of orthopedic and trauma surgery, Ramaioli and Pagani[3] found that 10 mg of 1% bupivacaine without adrenalin provided 135 minutes of spinal anesthesia for hip and femur operations, which compares favorably with our duration of 143 minutes for a similar dose. Comparison of the duration of spinal anesthesia between various studies is difficult due to lack of standardization of the manner and site of testing for termination of anesthesia. Our arbitrary choice of Allis forceps clamping in the suprapubic area as the endpoint of anesthesia cannot be compared with tests for duration of anesthesia in ankle or foot surgery.

Ramaioli and Pagani also found that duration of spinal anesthesia was a function of milligram dose of local anesthetic agent, reporting that bupivacaine anesthesia of 135 minutes with 10 mg increased to 350 minutes with 40 mg. Their maximum duration was 480 minutes (8 hours of spinal anesthesia) produced by 40 mg of bupivacaine and 0.5 mg adrenalin for leg and foot operations (16 cases) without apparent increase in adverse or toxic effects.

Lack of complete muscle paralysis in the area of spinal anesthesia may be desirable for obstetric or urologic anesthesia when abdominal muscle contraction by the patient is helpful, as in obstetric delivery or spontaneous-voiding x-ray. However, bupivacaine spinal anesthesia, regardless of dose, did not always provide a reduced motor blockade, but did provide in all cases satisfactory muscle relaxation for inguinal hernia repair.

We conclude that the results obtained with bupivacaine and tetracaine spinal anesthesia are clinically the same (except for an occasional decreased motor block with bupivacaine) when equal hyperbaric doses are used for similar surgical conditions.

REFERENCES

1. Moore DC, Bridenbaugh LD, Bridenbaugh PO, et al: Bupivacaine hydrochloride: laboratory and clinical studies. Anesthesiology 32:78-83, 1970

2. Szappanyos GG: The utilization of Marcaine (LAC-43) in spinal and epidural anaesthesia. Anaesthesist 18:330-333, 1969

3. Ramaioli F, Pagani I: Experience with 1% hyperbaric bupivacaine in 321 cases of spinal anesthesia for orthopedic and traumatological surgery. Minerva Anesthesiol 38:1-12, 1972

4. Pietrobono P, Maggi U: Spinal anaesthesia with hyperbaric bupivacaine: an old technique for a modern anaesthesia (observations on 300 cases). Acta Anaesthesiol 22:461-476, 1971

Anaphylaxis: Etiology and Guidelines for Management

DEAN H. MORROW, MD*
ROBERT R. LUTHER, MD†

The successful management of anaphylaxis requires a thorough understanding of this syndrome and the application of various therapeutic agents. Although the mechanisms responsible for human anaphylaxis are not fully known, sufficient data and clinical experience are available to guide the anesthesiologist faced with this medical emergency.

THE term "anaphylaxis" was introduced by Poitier and Richet in 1902 to describe the syndrome of shock and subsequent death which occurred in dogs following reinjection of the poison of the sea anemone.[1] Since that time, use of the term has broadened to include unusual or exaggerated hypersensitivity reactions to a variety of drugs and other substances.[2] Of particular importance to the anesthesiologist is the fact that anesthetic agents,[3-8] anesthesia adjuncts,[9,10] and other materials to which the patient may be exposed during operation[11-15] are now known to be capable of producing anaphylaxis.

Although the precise mechanisms underlying human anaphylaxis are not fully known, sufficient data are available to support a clinically useful explanation and basis for therapy. These considerations constitute the basis for this review, which is presented to aid the anesthetist dealing with anaphylaxis in his practice or as a member of the team responding to this medical emergency.

I. The Theoretic Basis for Anaphylaxis.

Systemic anaphylaxis is the most dramatic and dangerous hypersensitivity reaction and may cause death within minutes. This syndrome consists of a highly variable symptom complex including at least some of the following: conjunctivitis, vasomotor rhinitis, pilomotor erection, pruritic urticaria, angioedema, various gastrointestinal disturbances, laryngeal edema, bronchospasm, hypotension, arrhythmias, cardiac arrest, coma, and death. In fatal anaphylaxis, physiologic disturbances of the cardiovascular and respiratory systems predominate and frequently occur early.

The clinical signs, severity, progression, and duration of an anaphylactic reaction are highly unpredictable. The initial signs and symptoms do not necessarily reflect the severity, duration, or ultimate progression of the reaction. Anaphylaxis may be limited to a single symptom or may progress to cardiovascular and respiratory collapse within minutes. Fatal anaphylaxis may occur without milder premonitory symptoms and may be manifest only by rapidly progressive laryngeal edema and profound cardiovascular collapse, refractory to all treatment.

The duration of a reaction and any of its components varies from minutes to a day or longer. Appropriate immediate therapy may terminate the entire symptom complex quickly; however, laryngeal edema and hypotension may persist for hours or days despite appropriate therapeutic measures. Death may intervene at any time. Because the clinical spectrum of anaphylaxis is as wide as patient responses are variable, any systemic manifestation must be considered the forerunner of a potentially lethal process and be treated vigorously.

*Professor, Department of Anesthesiology, Baylor College of Medicine, Houston, Texas 77030.

†151 E. Palatine Road, Palatine Illinois.

Paper received: 2/20/76

Accepted for publication: 3/9/76

Anaphylactic reactions may occur following the administration of an exogenous antigenic stimulus. The time from antigenic challenge to the onset of a reaction is variable but typically occurs within 30 minutes. On the other hand, delays of an hour or more are possible, depending upon various factors, including the rate at which the antigen reaches the circulation.

The physiologic alterations of systemic anaphylaxis are mediated by various endogenous, pharmacologically active agents, the release of which is the result of complex antigen-antibody interactions at the cellular level. Anaphylaxis may occur in any subject appropriately sensitized to a particular antigen. Importantly, negative skin testing, negative history, and uneventful previous exposures to the antigen do not preclude the possibility of an anaphylactic type of reaction.[16]

When a susceptible individual is first exposed to a *specific* antigen, antigen-specific immunoglobulin E (IgE; reagin) antibodies are formed which will interact only with that particular antigen. These IgE antibodies are cytophilic and selectively attach to the cell membranes of circulating basophils and tissue mast cells. Subsequent exposure to the specific antigen results in an antigen-antibody interaction believed to be initiated by the bridging of 2 adjacent IgE molecules on the membranes of those cells. This bridging induces a complex series of intramembrane and intracellular events, which culminate in the release of histamine and the slow-reacting substance of anaphylaxis (SRS-A) from the cell. These mediators in turn may directly elicit local and systemic pharmacologic effects, cause the release of other mediators, or activate reflexes that ultimately produce the clinical picture of anaphylaxis.

The Role of Histamine.—Histamine is found in several mammalian tissues. In man, the presence of histamine in mast cells and basophils is most important. Histamine can cause bronchial constriction, increased capillary permeability, and vasodilation. Experimentally administered histamine produces rhinitis and bronchoconstriction, as well as headache, pruritus, blushing, and hypotension. By virtue of its presence in the metachromatic granules (as a protein-heparin-histamine complex) of mast cells and basophils, and the physiologic responses it elicits, histamine is believed to be a major mediator of anaphylaxis. The end-organ responses to histamine can be moderated or blocked by pharmacologic doses of antihistamine given before the histamine is released.

Slow-Reacting Substance.—SRS-A, a lipid synthesized and released in response to the antigen-antibody interaction, causes constriction of bronchial smooth muscle *in vitro* and has been shown to increase capillary permeability (wheal formation) after intracutaneous injection. Experimentally, SRS-A is released from human lung (rich in mast cells) which has been pretreated with IgE and then challenged either with anti-IgE or specific antigen. Since SRS-A can be released from immunologically challenged human lung, and because of its pharmacologic action on bronchial smooth muscle, it is believed to play an important role in human allergic asthma and perhaps anaphylaxis.

The origin of SRS-A released following an immunologic challenge is not known with certainty but is presumed to be mast cells and basophils. SRS-A release is enhanced by cholinergic agonists and can be moderated or blocked experimentally by anticholinergic agents.[17] Whether anticholinergic-related alterations in the release of SRS-A have a place in the treatment of human anaphylaxis has yet to be clarified.

This release of chemical mediators is an energy-dependent process related to alterations in the levels of intracellular cyclic adenosine-3′5′-monophosphate (cAMP). Beta-adrenergic agonists, for example epinephrine, isoproterenol, and other agents which activate the cell membrane-bound adenyl cyclase system, cause an increase in intracellular cAMP and inhibit the release of histamine and SRS-A. Similarly, mediator release is inhibited by the methylxanthines, which reduce the degradation of cAMP by phosphodiesterase and thereby increase intracellular cAMP levels. Conversely, interventions capable of decreasing intracellular cAMP enhance the release of histamine and SRS-A. The specific intramembrane and intracellular biochemical processes underlying these inverse correlations, however, have not been defined.

II. Treatment of the Anaphylactic Syndrome.

Anaphylaxis must be promptly and vigorously treated. While the anesthesiologist may be familiar with the drugs used to treat

TABLE 1

Drugs Useful in Treating Anaphylaxis

Drug class/agents	Physiologic action	Indication
1. Adrenergic agonists		
Epinephrine	Alpha and beta agonist	IMMEDIATE AND INITIAL TREATMENT OF ALL ANAPHYLACTIC REACTIONS
Isoproterenol	Beta agonist	Bronchospasm and hypotention with low cardiac output
Methoxamine	Alpha agonist	Hypotension with decreased peripheral vascular resistance
Ephedrine	Alpha and beta agonist	Hypotension and laryngeal edema
Metaraminol	Alpha and beta agonist	Hypotension
2. Methylxanthines		
Aminophylline	Bronchiolar dilation	Bronchospasm not reversed by epinephrine
3. Anticholinergics		
Atropine	? inhibit release of mediators	As preoperative prophylaxis
Scopolamine	? inhibit release of mediators	As preoperative prophylaxis
4. Antihistamines		
Diphenhydramine	Histamine blockade	ALL ANAPHYLACTIC REACTIONS FOLLOWING EPINEPHRINE ADMINISTRATION.
		? as preoperative prophylaxis
5. Corticosteroids		
Hydrocortisone	Unknown	Anaphylactic reactions refractory to above therapies, especially persistent bronchospasm or hypotension.
		? as preoperative prophylaxis

Adapted from Kelly and Patterson.[16]

anaphylaxis, he may not be thoroughly familiar with their application in this potential catastrophe.

A. General Pharmacologic Principles.

The therapy of anaphylaxis is based on empiric clinical effectiveness and, more recently, some understanding of the fundamental actions of 5 general classes of drugs: (1) adrenergic agonists, (2) methylxanthines, (3) anticholinergics, (4) antihistamines, and (5) corticosteroids (table 1).

1. Adrenergic agonists.—These are agents which evoke physiologic responses similar to those produced by efferent sympathetic (adrenergic) nerve activity. They are further categorized on the basis of their physiologic effects. Adrenergic agents producing primary effects on the heart and lungs are classified as *beta agonists;* those producing primary effects on the peripheral vasculature are classified as *alpha agonists.* Some agents produce both effects and are said to have a mixed action.

With reference to anaphylaxis, useful beta-agonistic responses include bronchodilation, increased myocardial contractility, increased heart rate, and constriction of the muscular arterioles with redistribution of blood to the central circulation. Beneficial alpha-agonistic responses include cutaneous, mucosal, and splanchnic vasoconstriction with increased total systemic vascular resistance. The increased myocardial contractility and heart rate increase cardiac output, which in combination with the increased total systemic vascular resistance elevates blood pressure and improves perfusion.

A spectrum of adrenergic agonistic drugs is available for treatment of anaphylaxis. These range from isoproterenol, a pure beta agonist, to methoxamine, a drug producing pure alpha stimulation. However, epinephrine, a drug with mixed action, is the agent of choice for the early treatment of anaphylaxis. The precise mechanisms responsible for the efficacy of epinephrine in reversing rhinitis, urticaria, bronchoconstriction, and hypotension during anaphylaxis are not known. However, these beneficial therapeutic effects are attributed to concomitant beta- and alpha-agonistic effects on the heart, lungs, and peripheral vasculature, in addition to a beta-effector-mediated increase

in the intracellular cAMP of mast cells and basophils.

As developed above, increased intracellular cAMP is correlated with a reduction in the release of histamine and SRS-A. The importance of the cellular effect of epinephrine in treating anaphylaxis probably depends on the stage of anaphylaxis at which the drug is administered. Early in the clinical syndrome, epinephrine should effectively decrease mediator release. After maximal mediator release has occurred, however, epinephrine would be less beneficial.

Other adrenergic-agonistic drugs that may have a place in treating anaphylaxis, particularly in patients in whom the use of epinephrine is contraindicated because of a concurrent medical problem, are listed in table 2. For example, in an elderly patient with advanced coronary atherosclerosis and myocardial ischemia, the selective alpha-effector response of methoxamine *might* be considered therapeutically preferable to epinephrine to treat hypotension secondary to anaphylaxis. However, in deciding to use this agent to avoid the cardiac stimulation of epinephrine, one would have to accept loss of beta-mediated effects on the bronchial smooth muscle, as well as the effects of epinephrine in decreasing histamine and SRS-A release.

Similarly, profound bronchospasm *without hypotension* might best be treated by the pulmonary beta-effector action of isoproterenol causing bronchiolar dilation. In this instance, however, diligent ECG monitoring would be obligatory to detect cardiac arrhythmias that may result from isoproterenol administration.

Patients under therapy for intercurrent medical problems which might preclude or alter the anticipated responses to epinephrine and other adrenergic-agonist agents should also be considered carefully. For example, hypertensive patients under treatment with the adrenergic neuronal blocking agents reserpine or guanethidine might exhibit accentuated beta- and alpha-adrenergic physiologic responses to usual doses of epinephrine. Similarly, patients in whom beta blockade had been established by the administration of propranolol might require unusually large doses of epinephrine to obtain relief of bronchospasm and/or enhanced cardiac activity during the treatment of anaphylaxis. As with any form of treatment, the selection of subjects is dependent upon medical judgment.

2. Methylxanthines.—Intravenous methylxanthines, in particular aminophylline, have been found useful in the treatment of anaphylaxis. This use is based on the ability of these drugs to relax bronchiolar smooth muscle and to increase cardiac output. Thus, these actions of the methylxanthines mimic the beta actions of the adrenergic agonists. The xanthines are more effective in decreasing pathogenic bronchospasm, such as that induced by histamine, serotonin, or acetylcholine, although the mechanism for this action is not known.[18]

These agents increase cardiac output through a direct action on myocardial contractility. At the peripheral vascular level, the xanthines produce vasodilation. In any given patient, the systemic arterial blood pressure response is determined by the degree to which augmented cardiac output compensates for the xanthine-induced decrease in peripheral resistance. This hemodynamic interaction is of particular importance in deciding whether to use xanthines in anaphylactic situations, including both bronchospasm and hypotension.

At the cellular level, the methylxanthines are known to inhibit phosphodiesterase, the enzyme responsible for the degradation of cAMP. By virtue of this action, xanthine administration is followed by increased intracellular cAMP. In anaphylaxis, treatment with methylxanthines theoretically would reduce the release of histamine and SRS-A following an antigenic challenge.

3. Anticholinergics.—Drugs which act at the receptors of tissues and organs by competitively blocking the action of acetylcholine released from cholinergic postganglionic autonomic nerves, are referred to as cholinergic blocking agents or anticholinergics. This group includes atropine and scopolamine, two drugs familiar to the anesthesiologist.

Bronchiolar smooth muscle is slightly relaxed by both atropine and scopolamine. In man, the duration of this action is longer after scopolamine. Additionally, the anticholinergic drugs reduce the mucus flow and ciliary movement in the trachea. These actions of the anticholinergics on the pulmonary tree are ascribed to inhibition of locally released acetylcholine secondary to efferent vagus nerve activity.

Although the bronchiolar dilatory action of the anticholinergics has not been widely used in the treatment of bronchial asthma, it is known that these drugs will directly

TABLE 1

Drugs Useful in Treating Anaphylaxis

Drug class/agents	Physiologic action	Indication
1. Adrenergic agonists		
Epinephrine	Alpha and beta agonist	IMMEDIATE AND INITIAL TREATMENT OF ALL ANAPHYLACTIC REACTIONS
Isoproterenol	Beta agonist	Bronchospasm and hypotention with low cardiac output
Methoxamine	Alpha agonist	Hypotension with decreased peripheral vascular resistance
Ephedrine	Alpha and beta agonist	Hypotension and laryngeal edema
Metaraminol	Alpha and beta agonist	Hypotension
2. Methylxanthines		
Aminophylline	Bronchiolar dilation	Bronchospasm not reversed by epinephrine
3. Anticholinergics		
Atropine	? inhibit release of mediators	As preoperative prophylaxis
Scopolamine	? inhibit release of mediators	As preoperative prophylaxis
4. Antihistamines		
Diphenhydramine	Histamine blockade	ALL ANAPHYLACTIC REACTIONS FOLLOWING EPINEPHRINE ADMINISTRATION.
		? as preoperative prophylaxis
5. Corticosteroids		
Hydrocortisone	Unknown	Anaphylactic reactions refractory to above therapies, especially persistent bronchospasm or hypotension.
		? as preoperative prophylaxis

Adapted from Kelly and Patterson.[16]

anaphylaxis, he may not be thoroughly familiar with their application in this potential catastrophe.

A. General Pharmacologic Principles.

The therapy of anaphylaxis is based on empiric clinical effectiveness and, more recently, some understanding of the fundamental actions of 5 general classes of drugs: (1) adrenergic agonists, (2) methylxanthines, (3) anticholinergics, (4) antihistamines, and (5) corticosteroids (table 1).

1. Adrenergic agonists.—These are agents which evoke physiologic responses similar to those produced by efferent sympathetic (adrenergic) nerve activity. They are further categorized on the basis of their physiologic effects. Adrenergic agents producing primary effects on the heart and lungs are classified as *beta agonists;* those producing primary effects on the peripheral vasculature are classified as *alpha agonists.* Some agents produce both effects and are said to have a mixed action.

With reference to anaphylaxis, useful beta-agonistic responses include bronchodilation, increased myocardial contractility, increased heart rate, and constriction of the muscular arterioles with redistribution of blood to the central circulation. Beneficial alpha-agonistic responses include cutaneous, mucosal, and splanchnic vasoconstriction with increased total systemic vascular resistance. The increased myocardial contractility and heart rate increase cardiac output, which in combination with the increased total systemic vascular resistance elevates blood pressure and improves perfusion.

A spectrum of adrenergic agonistic drugs is available for treatment of anaphylaxis. These range from isoproterenol, a pure beta agonist, to methoxamine, a drug producing pure alpha stimulation. However, epinephrine, a drug with mixed action, is the agent of choice for the early treatment of anaphylaxis. The precise mechanisms responsible for the efficacy of epinephrine in reversing rhinitis, urticaria, bronchoconstriction, and hypotension during anaphylaxis are not known. However, these beneficial therapeutic effects are attributed to concomitant beta- and alpha-agonistic effects on the heart, lungs, and peripheral vasculature, in addition to a beta-effector-mediated increase

in the intracellular cAMP of mast cells and basophils.

As developed above, increased intracellular cAMP is correlated with a reduction in the release of histamine and SRS-A. The importance of the cellular effect of epinephrine in treating anaphylaxis probably depends on the stage of anaphylaxis at which the drug is administered. Early in the clinical syndrome, epinephrine should effectively decrease mediator release. After maximal mediator release has occurred, however, epinephrine would be less beneficial.

Other adrenergic-agonistic drugs that may have a place in treating anaphylaxis, particularly in patients in whom the use of epinephrine is contraindicated because of a concurrent medical problem, are listed in table 2. For example, in an elderly patient with advanced coronary atherosclerosis and myocardial ischemia, the selective alpha-effector response of methoxamine *might* be considered therapeutically preferable to epinephrine to treat hypotension secondary to anaphylaxis. However, in deciding to use this agent to avoid the cardiac stimulation of epinephrine, one would have to accept loss of beta-mediated effects on the bronchial smooth muscle, as well as the effects of epinephrine in decreasing histamine and SRS-A release.

Similarly, profound bronchospasm *without hypotension* might best be treated by the pulmonary beta-effector action of isoproterenol causing bronchiolar dilation. In this instance, however, diligent ECG monitoring would be obligatory to detect cardiac arrhythmias that may result from isoproterenol administration.

Patients under therapy for intercurrent medical problems which might preclude or alter the anticipated responses to epinephrine and other adrenergic-agonist agents should also be considered carefully. For example, hypertensive patients under treatment with the adrenergic neuronal blocking agents reserpine or guanethidine might exhibit accentuated beta- and alpha-adrenergic physiologic responses to usual doses of epinephrine. Similarly, patients in whom beta blockade had been established by the administration of propranolol might require unusually large doses of epinephrine to obtain relief of bronchospasm and/or enhanced cardiac activity during the treatment of anaphylaxis. As with any form of treatment, the selection of subjects is dependent upon medical judgment.

2. Methylxanthines.—Intravenous methylxanthines, in particular aminophylline, have been found useful in the treatment of anaphylaxis. This use is based on the ability of these drugs to relax bronchiolar smooth muscle and to increase cardiac output. Thus, these actions of the methylxanthines mimic the beta actions of the adrenergic agonists. The xanthines are more effective in decreasing pathogenic bronchospasm, such as that induced by histamine, serotonin, or acetylcholine, although the mechanism for this action is not known.[18]

These agents increase cardiac output through a direct action on myocardial contractility. At the peripheral vascular level, the xanthines produce vasodilation. In any given patient, the systemic arterial blood pressure response is determined by the degree to which augmented cardiac output compensates for the xanthine-induced decrease in peripheral resistance. This hemodynamic interaction is of particular importance in deciding whether to use xanthines in anaphylactic situations, including both bronchospasm and hypotension.

At the cellular level, the methylxanthines are known to inhibit phosphodiesterase, the enzyme responsible for the degradation of cAMP. By virtue of this action, xanthine administration is followed by increased intracellular cAMP. In anaphylaxis, treatment with methylxanthines theoretically would reduce the release of histamine and SRS-A following an antigenic challenge.

3. Anticholinergics.—Drugs which act at the receptors of tissues and organs by competitively blocking the action of acetylcholine released from cholinergic postganglionic autonomic nerves, are referred to as cholinergic blocking agents or anticholinergics. This group includes atropine and scopolamine, two drugs familiar to the anesthesiologist.

Bronchiolar smooth muscle is slightly relaxed by both atropine and scopolamine. In man, the duration of this action is longer after scopolamine. Additionally, the anticholinergic drugs reduce the mucus flow and ciliary movement in the trachea. These actions of the anticholinergics on the pulmonary tree are ascribed to inhibition of locally released acetylcholine secondary to efferent vagus nerve activity.

Although the bronchiolar dilatory action of the anticholinergics has not been widely used in the treatment of bronchial asthma, it is known that these drugs will directly

TABLE 2

Suggested Therapy for Anaphylaxis

Manifestation	Immediate treatment (use in order enumerated)	Supportive measures: Drug therapy	Supportive measures: Clinical monitoring
Minor			
Conjunctivitis Erythema Pruritus Rhinitis Urticaria	1. Epinephrine HCl, 0.3 ml of 1:1000 IM 2. Diphenhydramine HCl, 50 mg IV	Diphenhydramine HCl, 50 mg q 6 hr	Observe for response to therapy
Major			
Arrhythmias		Oxygen; vasopressors as needed; antiarrhythmic agents as needed	ECG monitoring
Bronchospasm	1. Epinephrine HCl, 0.3 ml of 1:1000 IM or IV 2. Diphenhydramine HCl, 50 mg IV (1 dose only) 3. Oxygen	Epinephrine HCl, 0.3 ml of 1:1000 IM; aminophylline, 250 mg IV over 10 min and 500 mg IV q 6 hr; IV solutions; hydrocortisone; oxygen	Observe for respiratory failure and monitor blood gases
Hypotension	1. Epinephrine HCl, 0.3 ml of 1:1000 IM or IV 2. Diphenhydramine HCl, 50 mg IV	Metaraminol bitartrate, 100 mg/1000 ml of 5% D/W; IV solutions; oxygen; isoproterenol (to improve low cardiac output hypotension)	Monitor blood pressure and blood volume; observe for cardiac insufficiency or arrhythmias; observe for renal failure
Laryngeal edema	1. Epinephrine HCl, 0.3 ml of 1:1000 IM or IV 2. Diphenhydramine HCl, 50 mg IV	Diphenhydramine HCl, 50 mg q 6 hr; ephedrine sulfate, 25 mg q 6 hr; hydrocortisone; oxygen	Observe for hypoventilation and monitor blood gases; endotracheal intubation or tracheostomy if necessary

Adapted from Kelly and Patterson.[16]

antagonize the bronchiolar muscle spasm produced experimentally by a number of substances, including histamine.[19] Further, recent evidence has indicated that atropine blocks the ability of cholinergic stimuli to enhance the cellular release of histamine and SRS-A.[17] This action of anticholinergics in inhibiting anaphylactic mediator release is attributed to blockade of cholinergic-mediated increases in cellular cyclic 3′,5′-guanosine monophosphate (cGMP).[20]

4. Antihistamines.—Pharmacologically, the antihistamines represent a broad group of drugs which block most of the actions of histamine through competitive affinity to specific receptors for which histamine is the agonist. There is no evidence that the antihistaminic drugs in any way inactivate or interfere with the synthesis of histamine. The efficacy of antihistamines in competitively blocking the effects of histamine is greatest in situations associated with a high level of circulating histamine. Clinical experience indicates that these drugs are less effective in situations where histamine is released in close proximity to specific receptor sites.

Although still in part theoretic, these data provide an explanation for the therapeutic efficacy of antihistamines in abolishing urticaria associated with circulating histamine and the relative ineffectiveness of these drugs in bronchospasm accompanying human anaphylaxis where histamine is locally released, not systemically circulating. Alternatively, the limited effectiveness of antihistamines in relieving human bronchospasm may be attributed to the concomitant release of other chemical-mediator substances.[19]

5. Corticosteroids.—Although the corticosteroids have been recommended for use in anaphylaxis, the evidence justifying their use is equivocal. Steroids modify various clinical immune reactions such as homologous organ rejection and both immediate and delayed hypersensitivity. Further, steroids have been used successfully in treating and in preventing bronchial asthma and in moderating the ongoing hypotension and bronchospasm of anaphylaxis.[16] Although pretreatment with steroids has not yet been shown to alter the human anaphylactic response, experimentally induced systemic anaphylaxis is *decreased* by glucocorticoids.

Further, while the release of histamine in response to an allergic stimulus is unaffected or increased by glucocorticoids, the subsequent regeneration of histamine may be inhibited, presumably by a steroid-related action. Interestingly, the glucocorticoids do not modify the effects of histamine on smooth muscle or other cells.[21] Thus, despite the lack of a clear-cut basis for using steroids in the prevention or immediate treatment of anaphylaxis, presumptive evidence suggests potential benefits.

Again, it must be emphasized that epinephrine is the definitive therapeutic agent in the immediate treatment of anaphylaxis and that the substitution of other agents such as the steroids should be reserved for cases where epinephrine is relatively contraindicated.

B. Specific Therapy.

Table 2 categorizes the order, doses, and routes of administration for each of the 5 classes of drugs used to treat anaphylaxis.

COMMENT

The successful management of anaphylaxis is dependent on a thorough understanding of the syndrome and its prompt treatment. While there is a common misconception that anesthesia alters the classic signs of anaphylaxis and/or offers some protection against this syndrome, it has been recently pointed out by Bruce and Wingard[22] that available information and, in particular, data about the influence of newer general anesthetic agents on immune responses are insufficient to permit clinically useful conclusions. Indeed, between 1970 and the present, there have been more than 10 reports describing anaphylactic reactions during the perioperative period.[3-8,10,12-15] Were it possible to predict which patients would develop and what circumstances would lead to anaphylaxis, recent evidence about the cellular actions of anticholinergics and antihistamines might be used to greater advantage. Unfortunately, except for selected circumstances, the predictability of anaphylaxis remains obscure. Whether or not the incidence of anaphylactic reactions in anesthetized patients is increasing as has been suggested,[23] it would appear prudent for the anesthesiologist to help establish a program for the immediate treatment of anaphylaxis, including appropriate consultation and defined responsibilities. The success of such a program and its benefits to the patient can only be optimized by careful prior planning.

REFERENCES

1. Poitier P, Richet C: De l'action anaphylactique de certains venins. C R Soc Biol (Paris) 54:170-172, 1902

2. Patterson R, Schatz M: Factitious allergic emergencies: anaphylaxis and laryngeal "edema." J Allergy Clin Immunol 56:152-159, 1973

3. Watt JM: Anaphylactic reactions after use of CT 1341 (Althesin). Br Med J 3:205-206, 1975

4. Kessell J, Assem ESK: Correspondence, An adverse reaction to Althesin. Br J Anaesth 46:209, 1974

5. Notcutt WG: Adverse reaction to Althesin. Anaesthesia 28:673-674, 1973

6. John G: Cardiac arrest following induction with propanidid. Br J Anaesth 42:73-77, 1970

7. Thompson DS, Eason CN, Flacke JW: Thiamylal anaphylaxis. Anesthesiology 39:556-558, 1973

8. Davis J: Thiopentone anaphylaxis. Br J Anaesth 43:1191-1193, 1974

9. Hainsworth AM, Bingham W: An allergic circulatory collapse following the administration of muscle relaxants. Anaesthesia 25:105-109, 1970

10. Mandappa JM, Chandrasekhara PM, Nelvigi RG: Anaphylaxis to suxamethonium. Br J Anaesth 47:523-525, 1975

11. Maurer PH: Dextran, an antigen in man. Proc Soc Exp Biol Med 83:879-884, 1953

12. Lund N: Correspondence, Anaphylactic reaction induced by infusion of haemaccel. Br J Anaesth 45:929, 1973

13. Glauda NM, Henefer EP, Super S: Nonfatal anaphylaxis caused by oral penicillin: report of a case. JAMA 90:159-161, 1975

14. Spruill FG, Minette LJ, Sturner WQ: Two surgical deaths associated with cephalothin. JAMA 229:440-441, 1974

15. Velazquez JL, Gold MI: Anaphylactic reaction to cephalothin during anesthesia. Anesthesiology 43:476-478, 1975

16. Kelly JF, Patterson R: Anaphylaxis. JAMA 227:1431-1436, 1974

17. Kaliner M: IV. Immunologic mechanisms for release of chemical mediators of anaphylaxis from human lung tissue. Can Med Assoc J 110:431-435, 1974

18. Hume KM, Rhys-Jones E: The response to bronchodilators in intrinsic asthma. Q J Med 30: 189-199, 1961

19. Aviado DM: Regulation of bronchomotor tone during anesthesia. Anesthesiology 42:68-80, 1975

20. Barrett JP: Editorial views: Clinical epilog on bronchomotor tone. Anesthesiology 42:1-3, 1975

21. Mills LC: Adrenal cortex and adrenocortical hormones. Drill's Pharmacology in Medicine. Fourth edition. Edited by JR DiPalma. New York, McGraw-Hill Book Company, 1971, p 1542

22. Bruce DL, Wingard DW: Anesthesia and the immune response. Anesthesiology 34:271-282, 1971

23. Kelly AJ, Boman A: Correspondence, Anaphylaxis under anaesthesia. Anaesth Intensive Care 1:332-333, 1973

Neuromuscular Blocking Effects of Aminoglycoside Antibiotics on Fast- and Slow-Contracting Muscles of the Cat

H. R. ADAMS, DVM, PhD*
B. P. MATHEW, MS†
R. H. TESKE, DVM‡
H. D. MERCER, DVM§

The neuromuscular-blocking effects of neomycin, streptomycin, and gentamicin were examined in fast- and slow-twitch muscles of pentobarbital-anesthetized cats. These antibiotics were more effective in reducing indirectly stimulated contractions of the gastrocnemius muscle than of the ipsilateral soleus muscle in adult cats. Respiratory-depressant effects of these antibiotics were more closely associated temporally with effects on soleus than on gastrocnemius twitch. Neomycin was a more potent neuromuscular blocking agent in kittens >7 weeks old than in kittens <6 weeks old. Calcium ions were more effective in antagonizing the effects of neomycin on gastrocnemius than on soleus twitch; however, neostigmine was more effective in antagonizing the effects of neomycin on soleus than on gastrocnemius twitch. These data indicate a difference in responsiveness of fast- and slow-twitch muscles (fast > slow) to the neuromuscular-blocking effects of aminoglycoside antibiotics, and suggest that this may be related to a difference in the predominance of pre- and postjunctional inhibitory actions of these agents in the 2 muscle types.

ANTIBIOTICS structurally related to neomycin (aminoglycoside antibiotics) interfere with impulse transmission at the somatic myoneural junction.[1] The clinical importance of this neuromuscular-blocking effect is usually related to respiratory problems concurrent with the adminstration of neuromuscular-blocking agents and/or general anesthetics. Although Pittinger's group[2] reported an approximate 9% death rate in patients experiencing these problems, the clinical incidence of this adverse side effect is exceptionally low when the magnitude of antibiotic use is considered.

Experiments designed to examine the potency and characteristics of the neuromuscular-blocking effects of antibiotics have used fast-twitch skeletal muscle in nerve-muscle preparations.[3-7] However, some of the muscles that participate in respiratory

*Associate Professor, Department of Pharmacology, University of Texas Southwestern Medical School, Dallas, Texas 75235.

†Research Technician, Department of Pharmacology, University of Texas Southwestern Medical School, Dallas, Texas 75235.

‡Chief, Pharmacology-Toxicology Branch, Division of Veterinary Medical Research, Bureau of Veterinary Medicine, Food and Drug Administration, Beltsville, Maryland.

§Deputy Director, Division of Veterinary Medical Research, Bureau of Veterinary Medicine, Food and Drug Administration, Beltsville, Maryland.

This study was supported in part by research contract #72-312 from the Department of Health, Education and Welfare, Food and Drug Administration.

Paper received: 10/24/75

Accepted for publication: 12/4/75

movements exhibit slow-twitch characteristics, and studies have shown that neuromuscular-blocking agents can affect fast- and slow-twitch muscle differently.[8-12]

The purpose of the present study was to examine the neuromuscular-blocking properties of the aminoglycoside antibiotics, neomycin, gentamicin, and streptomycin (fig 1), in a gastrocnemius (fast-twitch) and soleus (slow-twitch) muscle preparation in anesthetized cats.

MATERIALS AND METHODS

Healthy adult cats of either sex, weighing between 2.5 and 3.8 kg, were anesthetized with sodium pentobarbital (35 mg/kg IP). Anesthesia was maintained during an experiment by periodic IV injection of small doses (1 to 2 mg/kg) of pentobarbital. The right femoral artery was catheterized for recording of blood pressure (Statham P23 pressure transducer) and the right femoral vein for injection of drugs. The trachea was cannulated and artificial respiration was maintained with room air by a Harvard respirator pump. In designated experiments, cats were allowed to breathe spontaneously and respiratory movements were monitored by use of a bellows-type pneumograph or by use of a thermocouple placed in the tracheal cannula.

Cats were prepared for monitoring indirectly stimulated muscle twitch of the m. gastrocnemius and m. soleus of the left hind limb, using a modification of a previously described technic.[13] The insertion of the m. gastrocnemius was isolated and connected by a stainless-steel wire to the rigid level of a precalibrated[14] force-displacement transducer (Grass FT.10) for recording isometric contractions. The soleus was carefully isolated from the anterior surface of the gastrocnemius mass, and its tendonous insertion was connected by silk suture to a precalibrated[14] force-displacement transducer (Grass FT.03) for measuring isometric contractions (fig 2). Approximately 100 gm resting tension was placed on the gastrocnemius and 25 gm on the soleus muscle.

During all experiments, muscle twitches of the left gastrocnemius and left soleus muscles were examined simultaneously by stimulation of the ipsilateral sciatic nerve. The sciatic nerve was exposed in the mid-thigh region of the hind limb, ligated, and stimulated peripheral to the ligation with shielded bipolar platinum electrodes at supramaximal voltage with shocks of 0.2 msec pulse duration delivered at a frequency of 12 shocks per minute (0.2 Hz) from a square-wave electrical stimulator (Grass S44). The leg was immobilized in extension by placing a stainless-steel intramedullary pin horizontally through the proximal tibia and clamping the pin at each end to stationary rods. The exposed portions of the

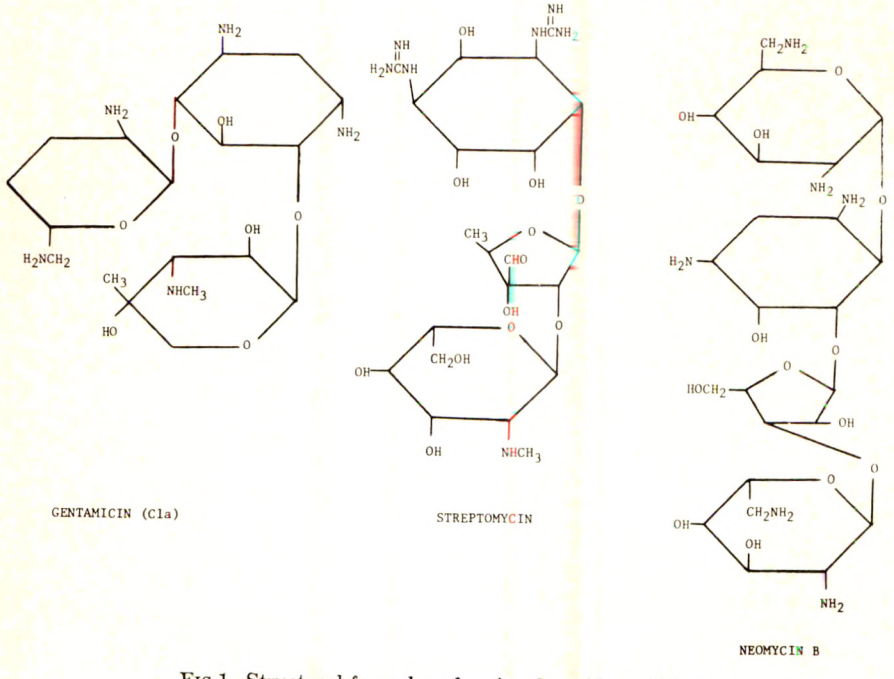


FIG 1. Structural formulas of aminoglycoside antibiotics.

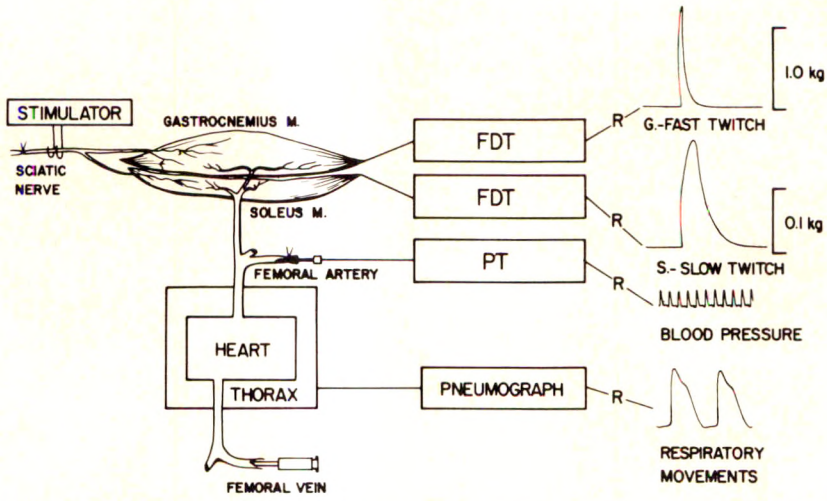


FIG 2. Schematic representation of a sciatic nerve-gastrocnemius and soleus-muscle preparation in anesthetized cats. FDT = force displacement transducer. PT = pressure transducer. R = recorder and amplifier: G. = gastrocnemius. S. = soleus.

muscles and the nerve were bathed in mineral oil and body warmth was maintained with a lamp. All recordings were made on a multichannel Grass model 7B polygraph.

Before proceeding with an experiment, care was taken with each preparation to obtain muscle twitch responses representative of each of the 2 muscle types. If the soleus twitch had an initial fast component or if a secondary slow component (characterized by prolonged relaxation) was observed in the gastrocnemius twitch, additional isolation was attempted at the proximal portion of the muscle bellies. Time was allowed for twitch to stabilize (at least 30 min) before proceeding with an experiment.

Initial studies used 23 cats to determine the dose-response effects of neomycin (n=9), streptomycin (n=10), and gentamicin (n=4). Time was allowed between injections for muscle twitch to return to preinjection values and to stabilize; an additional 20 to 30 minutes was allowed before proceeding with an experiment, to avoid pronounced cumulative effects of an antibiotic.[13] In several experiments, repeated IV injections of neomycin (5 mg/kg) were made at 3 to 4-minute intervals until gastrocnemius twitch was depressed by 90 to 100%. In some experiments, $CaCl_2$ or neostigmine was then administered and the recovery of muscle twitch in cats treated with one of these agents was compared to recovery in the control situation.

In addition, a sciatic nerve-calf muscle preparation was prepared in 11 kittens anesthetized with pentobarbital (28 to 34 mg/kg IP). Stimulation parameters were the same as for the adult cats. Contractions were measured with a Grass FT.03 force-displacement transducer and 25 gm resting tension was placed on the calf muscle. No attempt was made to separate the soleus from the gastrocnemius muscle in kittens. Six kittens were <6 weeks old and weighed between 300 and 430 gm (375.5 ± 21.6 gm, mean ± SE). Five kittens were >7 weeks old and weighed between 439 and 550 gm (477.8 ± 19.9 gm). Dose-response effects to IV administered neomycin (7, 14, and 28 mg/kg) were determined in each kitten and compared between the 2 age groups.

In the dose-response experiments, quantitation of neuromuscular blockade was calculated by measuring the maximum decrease in muscle twitch occurring after administration of an antibiotic and expressing this value in kg of generated tension or as a percent decrease from the preinjection (control) value. The influence of $CaCl_2$ and neostigmine on the effects of neomycin was quantified by normalizing muscle twitch depression, the maximal decrease in muscle twitch observed in each muscle being considered as 100% of the effect in that muscle. All other values obtained over time in that muscle were expressed as a percentage of the maximal effect.

All values are expressed as the mean ± 1 SE. Student's *t*-test was used for statistical comparison.

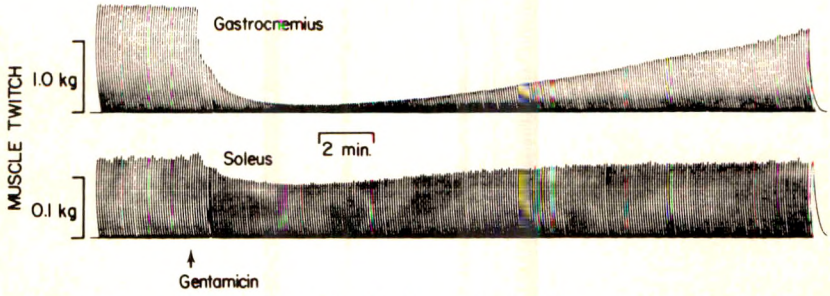


FIG 3. Typical responses of indirectly stimulated muscle twitches of the soleus and gastrocnemius muscles to the neuromuscular blocking effect of gentamicin (3 mg/kg, IV).

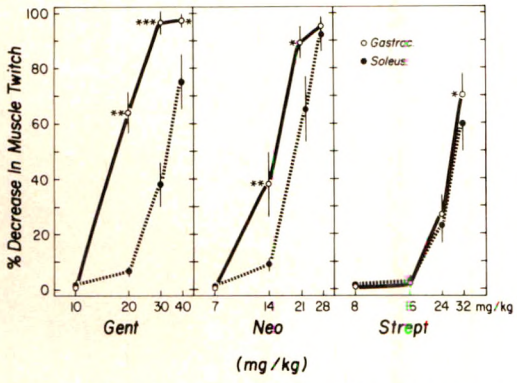


FIG 4. Effects of gentamicin (Gent), neomycin (Neo) and streptomycin (Strept) on indirectly stimulated muscle contraction of the soleus and gastrocnemius (Gastroc.) muscles. Each value is the mean ± SE of responses obtained in 4 (Gent), 9 (Neo), or 10 (Strept) cats. *, **, ***Difference between gastrocnemius and soleus was significant at the $p < 0.05$, $p < 0.005$, and $p < 0.001$ levels, respectively; paired t-test.

RESULTS

Indirectly stimulated contractions of the m. gastrocnemius and m. soleus in the anesthetized adult cat preparations usually exhibited typical fast- and slow-twitch characteristics, respectively. Approximately 10% of the preparations were not used, due to the apparent presence of fast-twitch fibers in the soleus or slow-twitch fibers in the gastrocnemius, even after additional attempts at surgical isolation.

Representative myograms obtained from a typical preparation are included in figure 2. The time to peak tension and total contraction time of 11 gastrocnemius muscles were 34.0 ± 1.1 msec and 260 ± 13.5 msec, respectively, whereas time to peak tension and total concentration time of the 11 corresponding soleus muscles were 100.9 ± 4.8 msec and 445.5 ± 18.1 msec, respectively. The gastrocnemius muscles generated between 1 and 1.5 kg of tension, whereas the soleus muscles generated between 0.1 and 0.4 kg of tension.

Intravenous administration of neomycin, gentamicin, or streptomycin consistently resulted in a decrease in the magnitude of indirectly stimulated muscle twitches of both gastrocnemius and soleus muscles. With each antibiotic studied, the neuromuscular-blocking effects were dose-related in both muscles; and in most cats examined, the effects on gastrocnemius twitch were more pronounced than on the corresponding soleus muscle. In 3 cats tested with streptomycin and in 2 cats tested with neomycin, the soleus was affected more than the corresponding gastrocnemius.

Typical recordings demonstrating the difference in responsiveness of the soleus and gastrocnemius muscles to an aminoglycoside antibiotic are shown in figure 3. Dose-response relationships with each antibiotic are shown in figure 4. In general, the order of potency of the antibiotics was neomycin > gentamicin > streptomycin. The differential effects on the 2 muscles were seen more consistently with neomycin and gentamicin than with streptomycin (fig 4). Absolute values of twitch responses obtained in the experiments with gentamicin are shown in table 1.

Previous studies have demonstrated that administration of Ca^{++} or a cholinesterase inhibitor is reliably effective in antagonizing the neuromuscular-blocking effects of aminoglycoside antibiotics in fast-twitch muscle-nerve preparations.[5-7,13] However, variable success has been reported with the use of these antagonists in clinical circumstances.[5-15] Experiments were included in the present study to determine if $CaCl_2$ and neostigmine were equally effective in antagonizing the effects of neomycin on fast- and slow-twitch muscles.

TABLE 1

Effects of Gentamicin on Indirectly Stimulated Contractions of the Gastrocnemius and Soleus Muscles

Gentamicin, mg/kg	Muscle	Tension, gm ± SE			p*
		Control	Response	Difference	
10 mg	Gastrocnemius	1340.0 ± 116.0	1330.0 ± 123.7	10.0 ± 10.0	>0.05
	Soleus	118.4 ± 9.4	116.0 ± 9.9	2.4 ± 1.1	
20 mg	Gastrocnemius	1386.8 ± 87.4	493.6 ± 66.6	893.2 ± 153.7	<0.005
	Soleus	118.0 ± 10.8	110.7 ± 10.3	7.3 ± 1.3	
30 mg	Gastrocnemius	1560.0 ± 100.6	26.6 ± 26.6	1533.4 ± 113.9	<0.001
	Soleus	122.9 ± 11.6	78.2 ± 6.2	44.7 ± 21.4	
40 mg	Gastrocnemius	1446.0 ± 156.7	26.0 ± 22.0	1420.0 ± 181.4	<0.005
	Soleus	129.3 ± 14.8	32.6 ± 25.7	96.4 ± 25.6	

*Student's paired t-test.

n = 4.

In 13 cats, 5 mg/kg of neomycin was injected IV every 3 to 4 minutes until gastrocnemius twitch was reduced by 90 to 100%. With this schedule, soleus twitch was concurrently decreased by 40 to 60%. Four of the cats served as controls and were not given additional injections. Muscle twitch amplitude at various time intervals was compared in the 4 control cats, in 6 cats given $CaCl_2$ (1.35 mEq Ca^{++}/kg, IV), and in 3 cats given neostigmine (100 μg/kg, IV) at the time of maximum depression of gastrocnemius twitch by neomycin. Since gastrocnemius twitch was consistently affected more than soleus, the effects of Ca^{++} and neostigmine on recovery of the muscles from the effects of neomycin were compared by normalizing muscle twitch depression. With each individual muscle, the maximum decrease in muscle twitch amplitude (90 to 100% in the gastrocnemius and 40 to 60% in the soleus) after injection of neomycin was considered to be 100% of the effect in that muscle. All other values over time of that individual muscle were expressed as a percentage of this maximum. Mean values (figs 5 and 6) show that neostigmine or Ca^{++} antagonized the neuromuscular-blocking effects of neomycin. For example, approximately 1 hour was required for either the gastrocnemius or soleus to recover from the

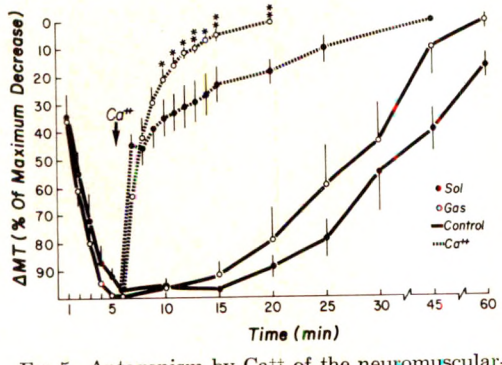


FIG 5. Antagonism by Ca^{++} of the neuromuscular-blocking effects of neomycin on indirectly stimulated contractions of the gastrocnemius (Gas) and soleus (Sol) muscles in anesthetized cats. Neomycin (5 mg/kg) was injected IV every 3 to 4 minutes until gastrocnemius twitch was reduced by 90 to 100%. Saline (solid lines; n = 4) or $CaCl_2$ (dashed lines; 1.35 mEq Ca^{++}/kg; n = 6) was then administered IV. Values are mean ± SE; results are normalized (see text). *, **Difference between gastrocnemius and soleus after administration of Ca^{++} was significant at the $p < 0.05$ and $p < 0.01$ levels, respectively.

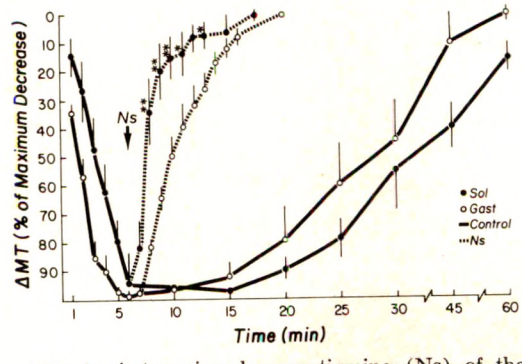


FIG 6. Antagonism by neostigmine (Ns) of the neuromuscular-blocking effect of neomycin on indirectly stimulated contractions of the gastrocnemius (Gast) and soleus (Sol) muscles. Neomycin (5 mg/kg) was injected IV every 3 to 4 minutes until gastrocnemius twitch was reduced by 90 to 100%. Saline (solid line; n = 4) or neostigmine (dashed line; 100 μg/kg; n = 3) was then administered IV. Values are mean ± SE; results are normalized (see text). *, **Difference between soleus and gastrocnemius after administration of neostigmine was significant at the $p < 0.05$ and $p < 0.01$ levels, respectively.

neuromuscular-blocking effects of repeated injections of neomycin, whereas after administration of Ca^{++} or neostigmine, the rate of recovery of muscle twitch height was greatly accelerated.

However, under the present experimental conditions, dissimilarities were seen in the relative effectiveness of Ca^{++} and neostigmine to antagonize the effects of neomycin on gastrocnemius and soleus contractions. Consistently, Ca^{++} was more effective than neostigmine in antagonizing the effects of neomycin in the gastrocnemius than in the soleus, although the gastrocnemius was affected by neomycin to a greater extent than was the soleus. Conversely, neostigmine was more effective than Ca^{++} in restoring normal muscle twitch height in the soleus than in the gastrocnemius (figs 5 and 6).

Four adult cats were allowed to breathe spontaneously and respiratory movements were monitored along with gastrocnemius and soleus twitches. An antibiotic (gentamicin, n=2; streptomycin, n=2) was repeatedly administered until apnea occurred. In each case, respiratory movements gradually decreased with succeeding doses of antibiotic but apnea did not occur until, or after, soleus twitch became completely depressed. A typical recording is shown in figure 7.

Studies in adult cats demonstrated that aminoglycoside antibiotics affected fast-twitch to a greater extent than slow-twitch muscle. This differential potency was examined further by the use of kittens. Skeletal muscles of kittens initially demonstrate slow-twitch characteristics until differentiation occurs during the first few weeks of life.[16] In the present study, the younger kittens were not as susceptible to the muscle twitch depressant effects of neomycin as were the older kittens (table 2).

TABLE 2

Neuromuscular-Blocking Effects of Neomycin on a Sciatic Nerve-Calf Muscle Preparation in Kittens

	Decrease in muscle twitch by neomycin, mg/kg		
Kitten age	7	14	28
	% ± SE		
< 6 wk (n = 6)	1.8 ± 1.2	13.4 ± 2.7	53.8 ± 6.4
> 7 wk (n = 5)	5.6 ± 0.8	52.1 ± 6.8	100.0 ± 0.0
Significance	<0.05*	<0.001*	<0.001*

*Student's *t*-test.

Control muscle twitch of <6-week-old and >7-week-old kittens averaged 127.5 ± 14.5 gm and 132 ± 10 gm, respectively.

DISCUSSION

Although the potential seriousness of antibiotic-induced respiratory paralysis in isolated cases is well established,[2] the incidence of such complications is exceedingly small in relation to the magnitude of antibiotic use. This can be attributed primarily to the low potency of the neuromuscular-blocking effects of these agents when compared to their antimicrobial activity. Aminoglycoside antibiotics have been found even less potent on slow-twitch muscle than on a fast-twitch muscle preparation similar to

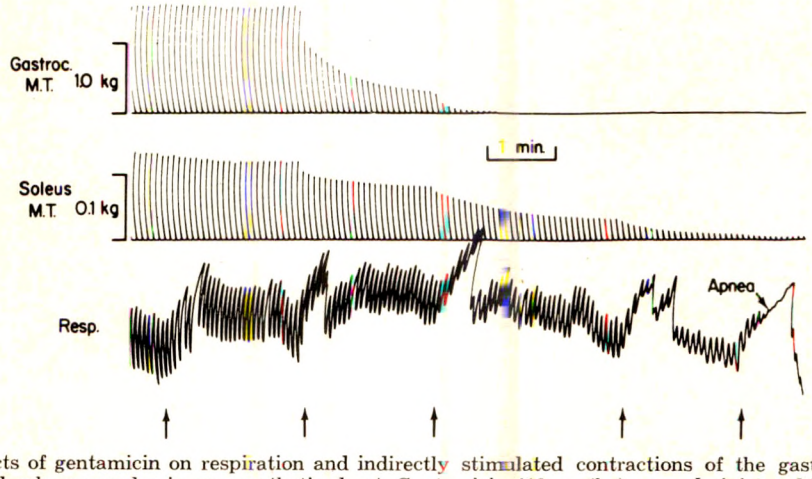


FIG 7. Effects of gentamicin on respiration and indirectly stimulated contractions of the gastrocnemius (Gastroc.) and soleus muscles in an anesthetized cat. Gentamicin (10 mg/kg) was administered IV at each arrow. M.T. = muscle twitch. Resp. = respiratory movements.

those commonly employed to examine these drugs.

In anesthetized adult cats, neomycin, gentamicin, and streptomycin were more effective in decreasing indirectly stimulated twitch of the fast-contracting gastrocnemius than of the slow-twitch soleus muscle. Since paired muscles of the same hind limb were tested concurrently by electrical stimulation of a common nerve trunk, it seems unlikely that observed differences in susceptibility of the gastrocnemius and soleus were due to variations in such factors as nerve stimulation, temperature, blood flow, or other secondary influences.[10] Rather, there seems to be a direct difference in responsiveness of the 2 muscle types to the neuromuscular-blocking effects of aminoglycoside antibiotics. This is further supported by findings in kittens. Skeletal muscle of newborn kittens reacts like slow-contracting muscle. Differentiation into respective slow- and fast-twitch types progresses with age and is usually complete or near complete in kittens >6 weeks of age.[16] In the present study, neomycin was relatively less potent in reducing the strength of indirectly stimulated twitch in kittens <6 weeks old.

Some respiratory muscles, like intercostals,[17] respond to drugs as slow-twitch muscles. In the present study, respiratory-depressant effects of gentamicin and streptomycin were more closely associated temporally with effects on soleus than on gastrocnemius twitch. This seems to support the contention that slow-contracting muscles are more resistant to the antibiotics studied. However, since contractile responses of respiratory muscles were neither individually nor directly examined, it is not known if the gradual diminution of ventilatory movements produced by repeated injection of an antibiotic reflects a decreasing fast muscle component (diaphragmatic)[10] in the presence of continued function of slow-twitch muscles or simply a resistance of respiratory muscles per se to the antibiotics.

Fast- and slow-twitch muscles are known to exhibit different sensitivities to clinically useful peripherally-acting muscle relaxants. With some exceptions, fast-twitch muscle is generally more susceptible to the depolarizing type of neuromuscular-blocking agent, whereas slow-twitch muscle is usually more responsive to the nondepolarizing curariform drugs.[8-12] Aminoglycoside antibiotics act postjunctionally to produce a nondepolarizing desensitization of the motor endplate; however, they are also believed to have a significant prejunctional action.[1,6] Recently, these drugs have been reported to inhibit Ca^{++} uptake in cholinergic nerves[18] and, presumably by this mechanism, to decrease the quanta of acetylcholine discharged from cholinergic fibers.[6,18]

In the present experiments, Ca^{++} had a relatively greater effect on recovery of the gastrocnemius from the effects of neomycin than it did on recovery of the soleus. Conversely, neostigmine hastened recovery of soleus twitch more than it did gastrocnemius twitch. These relative differences were consistently observed despite the fact that, before intervention with neostigmine or Ca^{++}, gastrocnemius twitch was invariably depressed more than the soleus, suggesting that in cats the postjunctional effect of aminoglycoside antibiotics dominates in slow-twitch muscles but prejunctional action is predominant in fast-twitch muscles.

Inhibition of Ca^{++} function in nervous and nonnervous tissues has been recognized as a pharmacologic property of the aminoglycoside antibiotics.[1,18,19-25] We have proposed that, in some excitable cell types, these antibiotics interfere with the uptake or binding of Ca^{++} by "competing" with the cation for negative-charged and superficial binding sites on cellular membranes.[19,20,25] Direct or indirect evidence for this postulate can be interpreted from data obtained from *in vivo* cardiovascular studies,[26] isolated arterial smooth muscles,[19-21,25] cholinergic neurons (sympathetic ganglion),[18] crab muscle fibers,[24] isolated sarcoplasmic reticulum fragments of skeletal muscle,[23] and isolated cardiac muscle.[22]

The difference in susceptibility of slow- and fast-twitch muscles to Ca^{++} and neostigmine during aminoglycoside antibiotic-induced neuromuscular blockade may be related to dissimilarities in prejunctional dependence upon Ca^{++} of respective motor nerves, nerve terminals of motor fibers innervating slow-twitch muscle perhaps being more resistant than analogous structures of fast-twitch muscle to the Ca^{++}-antagonistic properties of the neomycin-streptomycin antibiotics. However, the possibility cannot be excluded that postjunctional cholinergic receptors of fast-twitch muscle are more sensitive to the antibiotics than are receptors of slow-twitch muscle.

A difference in receptor configuration of fast- and slow-twitch muscles resulting in

different sensitivities to neuromuscular blocking agents has been suggested.[12] Although this remains to be established in relation to aminoglycoside antibiotics, present findings may partially explain why variable success has been encountered during attempts to reverse (clinically and experimentally) and even to demonstrate (experimentally) the neuromuscular-blocking effects of these antibiotics with different muscle types.[1,2,15,27] By inference, it seems possible that the difference in responsiveness of fast- and slow-twitch muscles to the clinically useful neuromuscular-blocking agents may also depend, at least in part, upon relative differences in the pre- and postjunctional inhibitory effects of these drugs.

REFERENCES

1. Pittinger CB, Adamson R: Antibiotic blockade of neuromuscular function. Annu Rev Pharmacol 12:169-184, 1972

2. Pittinger CB, Eryasa Y, Adamson R: Antibiotic-induced paralysis. Anesth & Analg 49:487-501, 1970

3. Naiman JG, Sakurai K, Martin JD Jr: The antagonism of calcium and neostigmine to kanamycin-induced neuromuscular paralysis. J Surg Res 5:323-328, 1965

4. Corrado AP, Ramos AO: Some pharacological aspects of a new antibiotic—kanamycin. Rev Bras Biol 20:43-50, 1960

5. Pandey K, Kumar S, Badola RP: Neuromuscular blocking and hypotensive actions of streptomycin, and their reversal. Br J Anaesth 36:19-25, 1964

6. Vital Brazil O, Prado-Franceschi J: The nature of neuromuscular block produced by neomycin and gentamicin. Arch Int Pharmacodyn 179:78-85, 1969

7. Stanley VF, Giesecke AH Jr, Jenkins MT: Neomycin-curare neuromuscular block and reversal in cats. Anesthesiology 31:228-232, 1969

8. Paton WDM, Zaimis EJ: The action of d-tubocurarine and of decamethonium on respiratory and other muscles in the cat. J Physiol 112:311-331, 1951

9. Jewell PA, Zaimis EJ: A differentiation between red and white muscle in the cat based on responses to neuromuscular blocking agents. J Physiol 124:417-428, 1954

10. Alderson AM, Maclagan J: The action of decamethonium and tubocurarine on the respiratory and limb muscles of the cat. J Physiol 173:38-56, 1964

11. Bonta IL, Goorissen EM: Different potency of pancuronium bromide on two types of skeletal muscle. Eur J Pharmacol 4:303-308, 1968

12. Marshall IG: The effects of three short-acting neuromuscular blocking agents on fast- and slow-contracting muscles of the cat. Eur J Pharmacol 21:299-304, 1973

13. Adams HR, Mathew BP: The cumulative neuromuscular blocking effect of neomycin. Arch Int Pharmacodyn 210:288-297, 1974

14. Freund FG, Merati JK: A source of errors in assessing neuromuscular blockade. Anesthesiology 39:540-542, 1973

15. Ream CR: Respiratory and cardiac arrest after intravenous administration of kanamycin with reversal of toxic effects by neostigmine. Ann Intern Med 59:384-387, 1963

16. Buller AJ, Lewis DM: Further observations on the differentiation of skeletal muscles in the kitten hind limb. J Physiol 176:355-370, 1965

17. Sakawala PB, Dillon JB: Mode of action of depolarizing agents. Acta Anaesthesiol Scand 3:83-101, 1959

18. Wright JM, Collier B: Inhibition by neomycin of acetylcholine release and ^{45}Ca accumulation in the superior cervical ganglion. Pharmacologist 16:285, 1974

19. Adams HR, Goodman FR, Lupean VA, et al: Effects of neomycin on tension and ^{45}Ca movements in rabbit aortic smooth muscle. Life Sci 12:279-287, 1973

20. Goodman FR, Weiss GB, Adams HR: Alterations by neomycin of ^{45}Ca movements and contractile responses in vascular smooth muscle. J Pharmacol Exp Ther 188:472-480, 1974

21. Adams HR, Goodman FR: Differential inhibitory effects of neomycin on contractile responses of various canine arteries. J Pharmacol Exp Ther 193:393-402, 1975

22. Adams HR: Direct myocardial depressant effects of gentamicin. Eur J Pharmacol 30:272-279, 1975

23. Fairhurst AS, Macri J: Aminoglycoside-Ca^{++} interactions in skeletal muscle preparations. Life Sci 16:1321-1330, 1975

24. Suarez-Kurtz G: Inhibition of membrane calcium activation by neomycin and streptomycin in crab muscle fibers. Pfluegers Arch 349:337-349, 1974

25. Adams HR, Goodman FR, Weiss GB: Alteration of contractile function and calcium ion movements in vascular smooth muscle by gentamicin and other aminoglycoside antibiotics. Antimicrob Agents Chemother 5:640-646, 1974

26. Adams HR: Cardovascular depressant effects of neomycin and gentamicin in rhesus monkeys. Br J Pharmacol 54:453-462, 1975

27. Sakawala PB, Dillon JB: The action of some antibiotics on the human intercostal nerve-muscle complex. Anesthesiology 20:659-668, 1959

"Acupuncture Anesthesia" — A Clinical Study

JEROME H. MODELL, MD*
PETER K. Y. LEE, MD†
HAL G. BINGHAM, MD‡
DONALD M. GREER, JR., MD§
MUTAZ B. HABAL, MD‖
Gainesville, Florida**

Forty-two patients who were to undergo plastic surgical procedures were asked whether they would accept acupuncture as a substitute for local anesthesia. Eight patients agreed to acupuncture; one of these had 2 operative procedures with acupuncture. Five of the 9 procedures were successful; the remaining 4 required conversion to local anesthesia.

After interviewing the patients, we felt that the success of "acupuncture anesthesia" was largely dependent on patient motivation, and that a patient may experience pain during surgical procedures without any change in facial expression or vital signs. We concluded that "acupuncture anesthesia" is of little value in our patient population at present. Its results are unpredictable; therefore, we anticipate that patient acceptance will be small.

IN 1958, in response to Chairman Mao Tse Tung's suggestion that traditional Chinese medicine is a "great treasure house" and should be combined with Western medicine and elevated to new heights, physicians in the People's Republic of China began using the traditional technic of acupuncture as anesthesia for surgical procedures. Enthusiasm for the technic, even in the People's Republic of China, grew slowly until the proletarian cultural revolution in 1966.†† Since that time there has been a concerted effort by physicians and patients in the People's Republic of China to adopt this combination of traditional and Western medicine whenever possible. Reports of operations performed successfully under "acupuncture anesthesia" in the People's Republic of China are commonplace in the American press.

One of us (Modell) was privileged to be a member of the Acupuncture Anesthesia Study Group of the Committee on Scholarly Communication with the People's Republic of China in May 1974. As such, he was the guest of the Chinese Medical Association for 22 days and observed surgical procedures performed under acupuncture. Some details of that visit have been published elsewhere.[1] Because of the questions raised in that report relating to whether a combination of acupuncture and surgery could be successful for patients in the United States, we conducted the following study.

PATIENT SELECTION AND METHODS

Patients were selected who were to have plastic surgical procedures that could be

††Unpublished report of Acupuncture Anesthesia Study Group of the Committee on Scholarly Communication with the People's Republic of China, May 1-22, 1974.

*Professor and Chairperson, Department of Anesthesiology.

†Visiting Research Professor, Department of Anesthesiology.

‡Professor and Chief, Department of Surgery, Division of Plastic Surgery.

§Assistant Professor, Department of Surgery, Division of Plastic Surgery.

‖Associate Professor, Department of Surgery, Division of Plastic Surgery.

**University of Florida College of Medicine, J. Hillis Miller Health Center, Gainesville, Florida 32610.

Paper received: 10/24/75

Accepted for publication: 1/6/76

converted easily to local anesthesia should acupuncture fail. Each patient was interviewed before the operation and given the choice of having the procedure performed under "acupuncture anesthesia" or under local anesthesia. All patients were told that if they felt uncomfortable at any time during the surgical procedure while under acupuncture, they could request that the acupuncture be terminated and local anesthetics be used. All questions asked by the patients were answered.

None of the patients received any form of premedication. Patients were given acupuncture along traditional meridians appropriate for the site of operation, using needles stimulated electrically with a stimulator capable of producing up to 9 volts at a frequency of 1 to 200 Hz. In general, current intensity and frequency were usually adjusted to the patient's tolerance. Acupuncture induction time was a minimum of 20 minutes. The surgical field then was prepared and draped and the operative procedure begun. The procedures were considered as either a success or failure, according to whether the patient requested that acupuncture be terminated and whether more than 2 ml of local anesthetic was used. In no case were analgesic drugs given.

RESULTS

Of 42 patients interviewed, 8 requested acupuncture. One of these patients had 2 procedures performed under acupuncture.

The first patient was a 20-year-old medical student who was to have a granuloma of the scalp excised. Needles were placed bilaterally at Chuan-Liao (SI-18), Tsu-Lin-Chi (GB-41), and Tsan-Chu (BL-2). In this patient, we did not attempt to increase the intensity of the stimulus to the patient's tolerance. Upon incision of the skin, the patient reported that he was undergoing an experience in "acupain." The acupuncture was terminated and a local anesthetic was infiltrated. The procedure continued without incident.

The second patient was a 45-year-old woman who had contacted one of the authors and requested that a rhinoplasty be performed under acupuncture anesthesia. She said that she had needed a rhinoplasty for a number of years but, because of her fear of both local and general anesthesia, had delayed the procedure. She reported that she was well motivated and wanted to volunteer for the study.

Acupuncture needles were placed bilaterally at Ho-Ku (LI-4), Chu-Chih (LI-11), and Tsu-San-Li (St-36). The patient underwent a 2½-hour rhinoplasty, including bilateral fracture of the nasal bones. Epinephrine (1:200,000) in saline solution was infiltrated from the beginning of the procedure to help control hemostasis.

Throughout the procedure, the patient frequently complained that the electrical stimulus of the acupuncture was too intense. Although she lay quietly on the operating table during much of the surgical procedure, she frequently voiced displeasure, reporting a feeling of intense pressure, particularly when tissues were spread rather than cut. When the nasal bones were to be fractured, the patient reported being quite uncomfortable, and 1 ml of 1% lidocaine with 1:200,000 epinephrine was injected on each side. During the procedure, the patient's pulse and blood pressure remained reasonably stable, despite discomfort.

At the conclusion of the procedure she apologized for any suggestion that she may have been uncomfortable and stated that she had not felt pain, was very pleased with the procedure, and would be happy to undergo a procedure under acupuncture in the future. This procedure, therefore, was considered successful. However, the anesthesiologist and surgeon were more impressed with the patient's endurance than with the analgesia afforded by the acupuncture.

Approximately 3 months later the patient was readmitted for revision of the tip of her nose. This second procedure also was performed under acupuncture but this time without complaint, incident, or changes in vital signs.

Patients 3, 4, and 5 were women, aged 26, 31, and 35, who were scheduled for augmentation mammoplasty. Acupuncture needles were placed bilaterally at Ho-Ku, Nei-Kuan (EH-6), and Tsu-San-Li. When the skin was incised, these patients complained of pain, and soon after the beginning of the procedure requested local anesthesia.

Patient 6 was a 28-year-old woman who had her earlobe reconstructed under acupuncture with no discomfort and no observable signs of pain. Needle placement was bilaterally at Ho-Ku and Shya-Chu (St-6).

Patient 7 was a 24-year-old woman who had needles placed bilaterally at Yang-Pai (GB-14) and Ho-Ku. A foreign body was

removed from the upper eyelid below the level of the levator, also with no reported discomfort or obvious signs of pain.

The 8th patient was a 35-year-old woman who had an augmentation mammoplasty. Needles were placed bilaterally at Ho-Ku, Nei-Kuan, and Tsu-San-Li. Because she complained of some discomfort upon incision through the right nipple, 0.5 ml of 1% lidocaine with 1:200,000 epinephrine was injected into each nipple. No other local anesthetic or analgesic agents were used. The remainder of the 2½-hour procedure was without incident and there was no change in vital signs at any time. The patient appeared calm, relaxed, and comfortable throughout, at times appearing to be dozing.

The patient did request that the intensity of the acupuncture be increased on several occasions but did not report a feeling of pain and did not request local anesthesia. Vital signs at these times were stable. At one point, she asked what was being done. She reported it was as though she were "being touched with a soldering iron," although it did not hurt. This coincided with the use of cautery deep on the chest wall. At the conclusion of the procedure, the patient reported she was comfortable. The surgeon and anesthesiologist considered the procedure an outstanding success. Because the procedure had gone so well, the patient was given a hand-held tape recorder to dictate her thoughts over the next 24 hours.

Pertinent excerpts from that tape are as follows:

"These thoughts have come upon me: 10:25 p.m. What pain I did feel is still vivid at this moment. As sensitive as my breasts—especially the nipple area—are, my greatest anxiety at this moment is fear of a complication that would warrant reopening or any extra surgical measures at this time. In effect, if I had not felt any pain in surgery, I would not fear going back into it.

"At first the entire incision really hurt, then I felt it most at one central point. I was able to tolerate it and from then on there were varying degrees of pain—sharp, short pains which seemed to be snips. I have skinned turkey legs not wanting to peel the film that keeps in the juice. I felt as if this is what was happening when the pockets were being made. It's hard to say why certain areas hurt more than others. Something happened on the left side and the pain was far up near my armpit around the area one would put a thermometer. It was hot and burning and a surprise. Several more times from then on I felt it. I don't think I could have tolerated a lot of it without squawking a little. I wanted to tolerate in silence as much as possible because I knew you would switch to local if I wanted and I didn't want this to happen until I could no longer control my reaction. There were periods of time when all I felt were pressure and pulling. It seems like those points allowed me to face the more painful areas, knowing that the worst would not last too long. As time went by I had such a desire to sleep I would relax and try to alienate the pain from my mind so as to rest and replenish courage. I was weakening. I felt and had such a feeling of dismay, not wanting to relate how I felt any more, just wanting to get it over.

"It is now 12:55 a.m. I am not really sleepy. I am going to relate, as best I can recall at this moment, my feelings mentally, as well as physically, pertaining to all aspects of the operation, as I could see it and feel it. Having never read about acupuncture, I was unaware of how it was done and didn't think electric currents were a part of it until Dr. Modell explained it, and before going to surgery Dr. Lee demonstrated what to expect. After being hooked up entirely and the current started, there were a few minutes of discomfort, ie, a heavy ache and my hand seemed to contract. After only a few minutes the aching subsided and the electrical current was soothing. I found myself wanting to relax and sleep but anxiety would not let me do so. I have described already the feeling through the surgery. As I seemed to feel more pain, I asked for more current. This seemed to help, although I'm not sure if it was the distraction of the surge of electricity or the lessening of the concurrent pain. At any rate it was helpful. At one time I reached a point while asking for current that it seemed too much and I asked for a lessening. Towards the end of the surgery it seemed as if my hands and left leg were getting tired and heavy. However, at no time did I experience anything pertaining to the acupuncture itself as painful."

DISCUSSION

Reports from the People's Republic of China suggest that "acupuncture anesthesia" is successful in over 90% of the patients in whom it is used. To interpret these figures, it is necessary to understand the

Chinese definition of "successful." The Chinese grade the results of "acupuncture anesthesia" in 4 categories: grades I through III are considered successful; grade I is used when the patient has little or no discomfort during the operative procedure and there are minimal changes in vital signs; grade II, when the patient has slight discomfort that can be controlled with small doses of narcotics and local anesthetics. Also, there may be moderate changes in vital signs. Grade III is used when the operation can be successfully completed, but the patient has periods of moderate to severe pain, changes in vital signs, and requires larger doses of parenteral medication and local anesthesia to complete the procedure; and grade IV when acupuncture fails and the operation must be abandoned or the patient given general anesthesia.[1]

The Chinese repeatedly point out that "acupuncture anesthesia" is still an experimental technic and represents an attempt to blend traditional Chinese medicine with Western medicine to improve health care for their people. They acknowledge that some of the present problems with "acupuncture anesthesia" are that many patients suffer incomplete analgesia, that muscle relaxation may be poor, that it does not abolish reflexes, and that patients frequently complain of feeling traction when viscera are manipulated, particularly during operations within the abdominal cavity.

The Chinese also stress the need for proper patient selection. "Acupuncture anesthesia" is not recommended for every patient; it is considered only when an accurate preoperative diagnosis has been established, when the surgical procedure promises to be uncomplicated, and when the patient agrees to have acupuncture after the advantages of "acupuncture anesthesia" and the disadvantages of general anesthesia have been explained. It is estimated that only 20% of patients in the People's Republic of China are operated on with "acupuncture anesthesia."[2]

In some patients, there is considerable preparation; patients who are to undergo thoracotomy must successfully complete a variety of breathing exercises for approximately a week before the operation. The anesthesiologist counsels the patient, and the surgeon and other patients in the hospital ward who have had "acupuncture anesthesia" tell him what they believe its advantages are. Also, each step of the surgical procedure is explained. Patients who are nervous or apprehensive are not considered suitable candidates. It is stressed repeatedly that for "acupuncture anesthesia" to be successful, the surgeon must be precise, rapid, and extremely gentle; tissues must be handled with a minimum of trauma, and retractors are seldom used in the wound. In addition to acupuncture, most patients in the People's Republic of China received approximately 100 mg of phenobarbital and 50 mg of meperidine preoperatively.

Observations in China.—The Acupuncture Anesthesia Study Group had the opportunity to observe, in depth, 48 patients who were preselected to have operations performed under "acupuncture anesthesia." The operations included such diverse procedures as tooth extractions, craniotomy for tumors, ophthalmologic surgery, tonsillectomy, thyroidectomy, pulmonary lobectomy, mitral commissurotomy, repair of ventricular septal defect with extracorporeal circulation, subtotal gastrectomy, ovarian cystectomy, abdominal hysterectomy, inguinal herniorrhaphy, and arthrotomy of the knee. Unfortunately, the Study Group did not observe a sufficient number of procedures in each category to be able to report any statistical significance regarding the success rate in any particular type of surgical procedure.

Of the 48 procedures seen, 25 patients (52%) fell into the category of grade I, and 10 patients (21%) into the category of grade II. The remainder (27%) were classified as grade III or IV.[1] There is no way to predict whether the same statistics would apply to a group of patients similarly selected and prepared in the United States. However, if one assumes that the American patients' responses to surgery and discomfort would be similar to those of the patients observed in the People's Republic of China, grade I results would be applicable to both populations. We also believe that many of our patients would accept a grade II result, but that grades III and IV would be unacceptable. Of the 9 procedures reported in our study, 4 would fit the grade I category. The rhinoplasty would be grade II, and 4 procedures would fit grade III or IV.

It was extremely difficult to interpret accurately the response of some of the patients observed in the People's Republic of China because, since none of them spoke English, the Study Group had to work through an interpreter. Many of the patients

reported a feeling of heaviness, pressure, and traction but denied pain. Because we were unable to question the patient directly, it was difficult to say with certainty whether the words "pain," "pressure," and "traction" were interpreted in the same way by patients and observers. At least 1 patient who had undergone a thyroidectomy described the feeling during operation as "pressure and traction." Upon detailed questioning through an interpreter after the operation, the patient admitted that she was unable to differentiate between what she called "pressure and traction" and what we called "discomfort" or "pain."

This difficulty in communication and the suggestion by some members of the Study Group that political motivation, education, conditioning, or some type of ethnic difference could explain the success of acupuncture in the People's Republic of China led to our current study. Our experience, particularly with patient 2 (rhinoplasty), certainly emphasized the importance of motivation in the success of the procedure. Our experience with patient 8 (augmentation mammoplasty) places considerable doubt on the ability of an observer to determine if a patient is experiencing pain. From all appearances, this patient was comfortable throughout the procedure. She had no change in blood pressure, pulse, respiratory rate or pattern; did not show any facial signs of discomfort; and did not appear to be peripherally vasoconstricted or to perspire. The 2 anesthesiologists who continually observed the patient were not able to detect any evidence of pain. However, the patient obviously felt pain, as evidenced by her very vivid and detailed report.

In spite of extensive research in the People's Republic of China, no definite physiologic mechanism for "acupuncture anesthesia" has been demonstrated.[3] We do not know if it produces anesthesia, analgesia, or hypalgesia. Perhaps hypalgesia is a more accurate description of what the Study Group observed. Another consideration was that needles were placed in traditional meridians and in "new experimental points," some of which were paraincisional, some segmental, and some appeared to be placed directly over or into a major nerve in an attempt to produce "acupuncture anesthesia." Seldom were needles placed in the same location for the same procedure in different patients. One professor in Peking reported, upon questioning, that a Peking surgeon gave the needle to the patient and let him insert and rotate it. He allegedly had a 90% success rate.

CONCLUSIONS

We conclude that the success of "acupuncture anesthesia" is largely dependent on patient motivation. It is well known that each patient's tolerance to pain is different.[4] It is entirely possible that a patient with a high threshold for pain and excellent motivation might be sufficiently distracted by the electrical stimulus of the needles from feeling pain during operation. It also is apparent from our small series that patients may experience pain without producing changes in their vital signs. Thus, it is virtually impossible, by purely clinical observation, to determine if the patient is experiencing pain. Pain appears to be a private experience of the patient which does not always lend itself to objective evaluation by the observer.

Our study suggests that "acupuncture anesthesia," analgesia, or hypalgesia is presently of little value for patients in the United States. Its results are unpredictable and general patient acceptance, therefore, is anticipated to be small. At present, the only clinical application we foresee would be for the patient who is to undergo a superficial procedure in which the risks of general anesthesia are not warranted and who reports a previous true hypersensitivity to a wide variety of local anesthetic agents. If such a patient also is well motivated, has a high pain threshold, and is willing to submit to the procedure, it is possible that he may be successfully operated on under "acupuncture anesthesia."

REFERENCES

1. Modell JH: Observations of "acupuncture anesthesia" in the People's Republic of China (editorial). Arch Surg 109:731-733, 1974

2. Bonica JJ: Anesthesiology in the People's Republic of China. Anesthesiology 40:175-186, 1974

3. Modell JH: A perspective of acupuncture. J Fla Med Assoc 63:123-128, 1976

4. Clark WC: Pain sensitivity and the report of pain: an introduction to sensory decision therapy. Anesthesiology 40:272-287, 1974

Perioperative Awareness and Recall

VOLKER EISELE, MD*
AVRON WEINREICH, MD†
STUART BARTLE, MD‡
New York, New York§

This study was designed to introduce a relevant stimulus at successive time intervals during the entire anesthetic period, including the pre- and postanesthetic periods. Using galvanic skin responses, the authors were able to recognize a plane of light anesthesia and arousal, at which time it is considered that sensory input might be perceived. Presenting to the patient a stimulus of some relevance, but one not likely to be psychically traumatic, they investigated the correlation between the ability to maintain an attention span and to recall in the postoperative period. No recall was obtained during the intraoperative period, the first occurrence of recall being in the immediate postanesthetic period and the incidence of recall increasing with increasing time intervals after the end of anesthesia. The authors conclude, however, that since intraoperative awareness without recall is a possibility, care should be taken to avoid emotionally disturbing auditory stimuli throughout the anesthetic procedure.

Is this a dream? Do I wake or sleep?
Keats

THE problem of awareness during anesthesia has existed since Horace Wells' inglorious failure during his first public demonstration of N_2O anesthesia. In 1908, Crile[1] reported a case of complete awareness during N_2O-O_2 anesthesia and recommended morphine and scopolamine as premedication to produce amnesia. In 1950, Winterbottom[2] reported the first case of awareness during a thiopental-muscle relaxant-N_2O-O_2 sequence. Since then, numerous case reports and studies have appeared in the literature.

Many of these retrospective reports were due to obviously inadequate anesthesia. Prospective studies on awareness during general anesthesia have failed to confirm convincingly the occurrence of recall of an intraoperative event.[3]

All studies reported so far have been incomplete in several aspects:

1. They do not indicate at which level of anesthesia a stimulus was presented.

2. The stimulus presented in all retrospective studies (with the exception of Levinson's work[4]) were irrelevant to the patient's well-being, whereas in those reports (including Levinson's) in which recall was reported, the stimulus was generally of a threatening nature.

3. No study has been undertaken in which a series of stimuli were presented systematically at different time intervals during the pre-, intra-, and postanesthetic periods.

The present study was designed to introduce a relevant stimulus at successive time intervals during the entire anesthetic period, including the pre- and postanesthetic periods. Employing the galvanic skin response (GSR),[5,6] we were able to recognize a plane of light anesthesia and arousal, at which time it is considered that sensory input might be perceived. We also presented

*Resident, Department of Anesthesia.
†Associate Professor, Department of Anesthesia.
‡Clinical Instructor in Psychiatry.
§Mount Sinai School of Medicine, New York, New York 10029.

Paper received: 7/21/75
Accepted for publication: 12/9/75

to the patient a stimulus of some relevance, but one not likely to prove psychically traumatic. Correlation between the ability to maintain an attention span and recall in the postoperative period was investigated.

METHOD

From June 1974 to January 1975, 250 patients undergoing various elective surgical procedures were studied. Ages ranged from 18 to 88 years. All patients were interviewed either at the time of the preoperative visit or on arrival in the induction room. At this time they were told that they would be given a number to remember either prior to induction, while they were anesthetized, or during the recovery period. Premedications used were atropine or scopolamine in combination with a sedative such as diazepam, secobarbital, Pantopon®, meperidine, or a combination of these agents given in standard doses. Anesthesia was induced in most cases with a sleep-dose of thiopental, in some cases with the addition of diazepam or Innovar®. Anesthesia was maintained by either inhalation agents such as halothane or enflurane or a neurolept technic using Innovar-fentanyl in combination with N_2O-O_2 and a muscle-relaxant (d-tubocurarine or pancuronium).

The 250 patients were divided into 5 equal groups, depending on the stage at which the stimulus was presented:

Group A: Prior to induction

Group B: Intraoperatively

Group C: Pre-extubation

Group D: On arrival in recovery room

Group E: Apparently awake

Group A was given an auditory stimulus; a random double digit number was chosen just prior to induction of anesthesia approximately 45 to 60 minutes after the administration of premedication. When the patients were in the recovery room and clinically awake and oriented to time and place, they were questioned about the number and were again questioned 24 hours later.

Patients in group B were given an auditory stimulus by means of earphones placed with the patients asleep to ensure a given constant amplitude of stimulus. A tape recorder delivered the message in an authoritative manner: "The doctor says you need number . . . ," followed by a double digit number. The message was repeated twice. This method of presentation was believed to be of some relevance to the patient without producing possible anxiety. Forty patients were given this input while clinically anesthetized with varying technics.

Ten patients of group B were considered separately. Atropine was omitted from the premedication because of its autonomic blockade activity; deep curarization was avoided because of its possible ganglionic-blocking effect; and anesthesia was maintained with N_2O-O_2 (70:30) and narcotic supplementation. These patients received their auditory stimuli during a period when GSR indicated autonomic activity. These responses are linearly related to the secretion of sweat and are an early response to stimuli normally absent during deep anesthesia. The autonomic activity as recorded by the GSR correlates with a period of arousal. The GSR was recorded with silver-silver chloride electrodes, placed on the surface of the 2nd and 4th middle phalanges. Input was recorded on a standard Beckman GSR coupler.

After termination of the anesthetic when the patients were clinically awake and oriented to time and place, they were asked: "Do you remember anything unusual the doctor said?" This was repeated on leaving the recovery room and again 24 hours later.

Group C patients were given an auditory stimulus at the termination of anesthesia prior to extubation. This was suggested to them at a time when they were able to follow verbal commands such as "lift your head," "open your eyes," "squeeze my hand." The message was delivered in an authoritative manner: "It is very important for you to remember number . . ." The patients were questioned about the number when they were clinically awake and oriented to time and place, and again 24 hours later.

Group D patients were given both an auditory and a visual stimulus consisting of a giant playing card (at the same time vocalizing the number appearing on the card) approximately 5 to 10 minutes after termination of anesthesia when they arrived in the recovery room. Also tested was their ability to maintain an attention span by having them observe the examiner's finger in front of their eyes as long as possible. The time of the attention span was recorded. These patients were questioned 1 hour later in the recovery room for any recall of either the auditory or the visual stimulus. If they

were not able to recall the number of the card, they were presented with a choice of 3 cards, including the one previously shown to them.

Group E patients were interviewed in the recovery room when they were considered clinically awake with a normal attention span. They were given the same auditory and visual stimulus as described for group D and were questioned about these stimuli approximately 1 hour later.

RESULTS (table 1)

1. All 50 patients in group A recalled the numbers presented prior to induction at 1 hour and 24 hours later, irrespective of the premedication and anesthetic agents.

2. None of the 50 patients in group B given the message by earphones, including the patients to whom the stimulus was given at an arousal period as indicated by GSR, had any recall, irrespective of premedication and anesthetic agents.

3. Four of the 50 patients in group C were able to recall the number given prior to extubation; 46 patients had no recall. All 4 patients with positive recall had thiopental induction followed by N_2O-O_2 with narcotic supplementation (Innovar® and fentanyl, 2 cases; meperidine, 2 cases) and a muscle relaxant (tables 2 and 3).

4. Of the 50 patients in group D, 28 had positive recall for the given number, 22 patients had no recall (tables 4 and 5). Mean attention span in the 28 patients with positive recall was 42.6 ± 13 seconds and in the 22 patients with no recall was 4.3 ± 2.4 seconds.

5. All 50 patients in group E recalled both the auditory and visual stimuli.

TABLE 1
Incidence of Recall in Groups A-E

Group	Time of input	Number of cases	Positive recall
A	Prior to induction	50	50 (100%)
B	Intraoperatively	50	0 (0%)
C	Pre-extubation	50	4 (8%)
D	On arrival in recovery room	50	28 (56%)
E	Apparently fully awake	50	50 (100%)

TABLE 2
Premedications and Recall of Patients in Group C

Premedication	Number of cases	Positive recall
Secobarbital/atropine	22	1
Diazepam/atropine	10	0
Pantopon/atropine	8	1
Meperidine/atropine	1	1
Meperidine/secobarbital/atropine	2	0
None	7	1
Total	50	4

DISCUSSION

The formation of a memory involves successive stages of registration: Information input leads to the formation of short-term memory, followed by consolidation and storage of a long-term memory. Whether a given input will lead to the formation of either a short-term or long-term memory (a memory "engram") depends upon the strength of the input and the sensory threshold at the time.[7]

It has been postulated that anesthetic amnesia occurs by impairment of the memory-consolidation process, presumably between the short-term and long-term memory formation and by attenuation of sensory transmission.[7]

When transient lightening of the anesthetic level coincides with an auditory stimulus of a highly emotional content, the possibilitiy of memory consolidation and later recall exists. The problem of recall of an

TABLE 3
Anesthetic Agents and Recall of Patients in Group C

Anesthetic agents	Number of cases	Positive recall
Thiopental—Halothane—N_2O	19	0
Thiopental—Enflurane—N_2O	6	0
Thiopental—Innovar-fentanyl—N_2O	21	2
Thiopental—N_2O	2	0
Thiopental—Meperidine—N_2O	2	2
Total	50	4

TABLE 4
Premedications and Recall of Patients in Group D

Premedication	Number of cases	Positive recall	No recall
Secobarbital/atropine	12	5	7
Diazepam/scopolamine	1	1	0
Diazepam/atropine	12	6	6
Pantopon/scopolamine	3	1	2
Pantopon/atropine	13	9	4
Meperidine/atropine	1	0	1
Meperidine/secobarbital/atropine	1	1	0
Diazepam/secobarbital/atropine	1	1	0
None	6	4	2
Total	50	28	22

TABLE 5
Anesthetic Agents and Recall of Patients in Group D

Anesthetic agents	Number of cases	Positive recall	No recall
Thiopental—Halothane—N_2O—	12	4	8
Thiopental—Enflurane—N_2O—	5	2	3
Thiopental—Innovar-fentanyl—N_2O—	23	15	8
Thiopental—N_2O	7	5	2
Thiopental—meperidine	1	1	0
Thiopental—diazepam—N_2O	2	1	1
Total	50	28	22

intraoperative event has never been a feature of deep inhalation anesthesia. Only fairly recently, with the advent of the thiopental-muscle relaxant-N_2O-O_2 technic and the concept of balanced anesthesia, have reports of recall of intraoperative events, usually of an anecdotal nature, appeared. The increased use of the neurolept-muscle relaxant sequence is partly due to its value in high-risk patients and as an alternative to repeated exposure to halothane.

The desire to maintain a high F_{IO_2} during anesthesia contributes to a reduction of the analgesic and amnesic effects of N_2O. In addition, the current concept of maintaining the P_{aCO_2} nearer to physiologic values negates the possible analgesic effects of hypocapnia suggested by Geddes and Gray.[8]

As a consequence, an inherent danger of the neurolept-muscle relaxant technic lies in an uneven anesthetic state, where an adequately anesthetized sensorium alternates with peaks of arousal, without the operator being alerted by the more obvious clinical signs of too-light anesthesia. It is during this period that the patient may be aware of external stimuli, if the stimuli are of a highly emotional or threatening content. They may be stored in some part of memory, producing anxiety, and possibly later emotional disturbance.[9]

While Guedel's stages for ether anesthesia still remain a yardstick for measuring anesthetic depth, and the EEG patterns obtained during anesthesia with other volatile agents provide repeatable levels, the neurolept technics have no equivalent staging; the EEG may even show an awake pattern,[10] while the clinical signs of autonomic activity are often difficult to interpret. In this situation, the GSR is a better indication of anesthetic depth.

None of the patients in group A (preinduction) showed anterograde or retrograde amnesia irrespective of premedication or anesthetic agents used. While previous work has demonstrated profound amnesic effects of scopolamine and diazepam, we were unable to demonstrate any amnesia for the preoperative period. As for diazepam, this may not be surprising, since others[11,12] have shown that dense anterograde amnesia is present only for 10 to 15 minutes after the IV injection, with less severe impairment existing up to one-half hour. We gave diazepam IM ± 1 hour before operation, when an amnesic effect would no longer be expected. The absence of retrograde amnesia following the various anesthetic technics used is in agreement with the findings of Dundee and Pandit,[13] who were unable to confirm the depressant effect of anesthetic agents on a consolidated memory.

We were unable to obtain any recall from patients in group B, whether "adequately" anesthetized or in a state of arousal. This is in contrast to the work of others in the field,[14-22] where seemingly innocuous and irrelevant information has been volunteered in the postoperative period by patients supposedly anesthetized, while undergoing surgical procedures.

Of the 50 patients in group C (pre-extubation period) 25 patients were anesthetized with a volatile agent (halothane or enflurane) and 25 were anesthetized with a thiopental-N_2O-O_2 technic supplemented by a narcotic agent (meperidine or fentanyl). All patients responded to verbal commands. No recall was obtained from patients anesthetized with a volatile agent, whereas 4 patients in the group anesthetized with a neurolept technic had positive recall. One of these 4 patients, on later questioning, was under the impression that the number was given to him during the operation itself.

Where an N_2O-O_2-muscle relaxant technic alone is employed, the incidence of recall has been reported as high,[23] and awakening is prompt upon withdrawal of N_2O. Similarly, with short-acting narcotic supplements, the patient awakes promptly and a high incidence of recall is reported. Those patients anesthetized with volatile agents would be expected to have suppression of memory consolidation for a considerable time after the termination of anesthesia as the agents slowly elute from the extravascular depots, re-enter the circulation, and prolong anesthesia.

These observations hold true in our comparison of results of groups C and D. The more time that elapsed following termination of the anesthetic, the higher the incidence of recall. At the termination of the anesthetic, only 4/50 in group-C patients had recall, while 28 patients in group D had positive recall. Approximately 2/3 of these patients had received neuroleptanesthesia and approximately 1/3, a volatile agent.

The postoperative attention span shows a close correlation with the memory-consolidation process and subsequent recall, those with a short attention span having no recall and those with a normal or long attention span having complete recall. The determination of the postoperative attention span represents a valuable measure of a patient's ability to recall information given at this time and is easily applicable to the clinical situation.

All patients in group E who appeared to be clinically awake were able to retain a memory of their given stimulus.

An anesthetic may be considered to start with the awake and medicated patients and continue through the various stages of anesthesia to the "awake" patient, who may be still emerging from his anesthetic, the results of which may be evident for as long as 2 weeks.[24]

The altered perception may range from total amnesia, dreams, and/or hallucinations, to a loss of 2-point discrimination. Memory, by definition, can only occur during a period of awareness; and where this occurs even momentarily during the course of an anesthetic, it must be regarded as inadequate anesthesia for that period.

We were not able to obtain any recall during the intraoperative period and in some instances even into the postoperative period when the anesthetic had been discontinued for some time. This does not mean that intraoperative awareness without recall is not a possibility. Attention should be given to careful and continuous observation of the patient's face throughout the surgical procedure whenever this is possible. A good anesthetic, light yet to be devised, would be invaluable.

We have been able to demonstrate time and again where a patient grimaces, wrinkles the forehead or moves his head, that where immediate contact is made by stroking the face or speaking reassuringly, the need for

further medication can usually be postponed. Surely this must be regarded as a stage of arousal and should it pass unnoticed either through inattention or because of lack of access to the patient's face, sensory input might be perceived, if not remembered, leading to cases of a Traumatic Neurotic Syndrome.[25]

It is our practice to induce with diazepam alone or supplement the induction of Thiopentone sodium with IV diazepam when a neurolept anesthetic technique is planned. The delay in recovery time is well worth the assurance that the likelihood of awareness and recall will be lessened.[26] Care should be taken during the operation to avoid emotionally disturbing auditory stimuli. Particular care is imperative in the pre-extubation period, and similar discretion is advocated in the recovery room, where confusion may exist for time and place, and events transposed in memory to the intraoperative period.

REFERENCES

1. Crile G: Autobiography. Edited by Grace Crile. Philadelphia, Lippincott 1947, vol I. p 197

2. Winterbottom EH: Insufficient anesthesia (correspondence). Br Med J 1:247-248, 1950

3. Scott DL: Awareness during general anaesthesia. Can Anaesth Soc J 19:173-183, 1972

4. Levinson BW: States of awareness during general anaesthesia. Br J Anaesth 37:544-546, 1965

5. Lykken DT, Venables PH: Direct measurements of skin conductance: a proposal for standardization. Psychophysiology 8:656-672, 1971

6. Weinreich A, Ruder E: Intraoperative awareness during neurolept anesthesia. Anesthesiology Review 3:29-32, 1976

7. Cherkin A, Harroun P: Anesthesia and memory process. Anesthesiology 34:469-474, 1971

8. Geddes IC, Gray TC: Hyperventilation for the maintenance of anesthesia. Lancet 2:4, 1959

9. Meyer BC, Blacher RS, Brown F: A clinical study of psychiatric and psychological aspects of mitral surgery. Psychosom Med 23:194-218, 1961

10. Parkhouse J: Awareness during surgery. Post Grad Med J 2:674-679, 1960

11. Clark PRF, Eccessly PS, Frisby JP, et al: The amnesic effect of diazepam (Valium). Br J Anaesth 42:690-697, 1970

12. Frumin MJ, Herekar V, Jarvik ME: The amnesic action of diazepam, scopolamine and narcotics in preanesthetic medication. Abstract of Scientific Papers, American Society of Anesthesiologists Annual Meeting, 1969, pp 129-130

13. Dundee JW, Pandit SK: Studies on drug-induced amnesia with intravenous anaesthetic agents in man. Br J Anaesth 26:164-166, 1972

14. Winterbottom EH: Insufficient anaesthesia (correspondence). Br Med J 1:247, 1950

15. Lancet Editorial, December, 1973, 2 p 1305

16. McKenna T, Wilton TNP, Anesthesia, 1973, 28, 599

17. Graff TD, Phillips OC: Consciousness and pain during apparent surgical anaesthesia. JAMA, 170:2069, 1959

18. Editorial. Br Med J 2:810, 1959

19. Editorial. Lancet, 2:1394, 1961

20. Editorial. Anesthesiology, 22:314, 1961

21. Alment EAJ: Consciousness during surgical operation (correspondence). Br Med J 2:1258, 1959

22. Bahl CP, Wadwa S: Consciousness during apparent surgical anaesthesia. Br J Anaesth, 40:289, 1968

23. Browne RA, Catton DV: Awareness during anaesthesia. Can Anaesth Soc J 20:763-767, 1973

24. Jaffe J, Bender M: Perceptual patterns during recovery from general anesthesia. J Neurol Neurosurg Psychiatry 14:316-321, 1951

25. Blacker RS: JAMA Vol 234, No 1, pp 67-68, Oct 6, 1975

26. Editorial. Lancet, pp 968-969, May 18, 1974

Severe Hypertension in a Child with Wilms' Tumor: A Case Report

MILTON L. COBB, MD*
ROBERT W. VAUGHAN, MD†
St. Louis, Missouri‡

Problems of management in a child with a large Wilms' tumor and severe uncontrolled hypertension presenting for anesthesia and operation included attempts to determine the etiology of the hypertension; identification of hazards produced by attempted rapid pharmacologic control of blood pressure; need for urgent operative intervention despite uncontrolled hypertension; and choice of anesthetic agent and technic.

THE association of Wilms' tumor (carcinosarcoma, embryoma, nephroblastoma, adenomyosarcoma) with hypertension was first reported in 1938 by Bradley and Pincoffs.[1] However, only 6 cases of severe hypertension (diastolic greater than 120 torr) in the child with Wilms' tumor have been reported.[1-6] No mention of this association or suggested management appears in the anesthetic literature. This report describes the anesthetic management of such a patient.

REPORT OF A CASE

A 27-month-old, 12.7-kg Caucasian boy was referred from another hospital for evaluation of hypertension associated with a large right-sided abdominal mass. During initial evaluation at the referring hospital, a venacavagram and an intravenous pyelogram were performed, revealing an abdominal mass displacing the right kidney downward and the inferior vena cava to the left of the midline. A chest roentgenogram was interpreted as normal, blood pressure was elevated (180/120 torr), and routine complete blood count and urinalysis were normal.

Following transfer, physical examination revealed an irritable thin child with a protuberant abdomen. Supine blood pressure was 210/140 torr in both arms; the pulse rate ranged from 100/minute (resting quietly) to 160/minute while crying. A firm, smooth, immobile mass was palpable in the right upper quadrant, extending vertically from the costal margin to the iliac crest and medially just across the midline. The extremities were warm and the palms of the hands constantly appeared flushed.

Laboratory values on the day of admission, including complete blood count, platelet count, serum electrolytes, blood urea nitrogen, serum liver enzymes, calcium, and phosphorus were all within normal limits. No evidence of mestastasis was found on chest or skeletal radiographs.

Attempts to control the blood pressure were begun immediately; intravenous and oral hydralazine, as well as intravenous diazoxide and furosemide were given. Nevertheless, over the next 36 hours, blood pressure varied from 170/120 torr to as high as 240/170 torr. Serum K^+ had fallen from 3.5 to 2.7 mEq/L in association with vigorous diuretic administration.

Because of concern for the complications of uncontrolled, sustained hypertension (especially a cerebrovascular accident),[3,7] it

*Assistant Professor.

†Associate Professor. (Current address: Department of Anesthesiology, University of Arizona School of Medicine, Tucson, Arizona.)

‡Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri 63110.

Paper received: 11/3/75

Accepted for publication: 12/1/75

was decided to proceed immediately with surgical extirpation of the tumor. Presumptive diagnosis was Wilms' tumor, although neuroblastoma and pheochromocytoma were considered possible. A urine spot test for vanillylmandelic acid had, however, been reported as negative. No premedication was administered because the patient was sedated from a previous injection (meperidine 12 mg) given for planned, but canceled, arteriography.

Upon arrival in the operating room, while resting quietly, the patient's blood pressure was 200/120 torr with a pulse of 100/minute. Anticipating the possibility of either severe hypertension or hypotension requiring pharmacologic control, both phentolamine and norepinephrine drips had been prepared. A careful inhalation induction with halothane-N_2O-O_2 proceeded without difficulty, and endotracheal intubation was easily accomplished without muscle relaxant.

A radial-artery cannula was placed as soon as the patient lost consciousness, and wide-bore intravenous lines (16 gauge) were established in both upper extremities. During induction, the blood pressure gradually decreased to 120/70 torr and remained between 110/60 and 140/80 torr throughout the 4-hour operative procedure. Anesthesia was maintained with halothane (1 to 1.5% inspired concentration) with manually controlled ventilation.

Operative resection included the tumor mass involving the right kidney plus the adjacent, normal-appearing adrenal gland. Five percent dextrose in lactated Ringer's solution was administered at a rate of 8 ml/kg/hr. Operative blood loss (approximately 150 ml) was replaced with warmed whole blood as the loss occurred. Upon completion of operation and discontinuance of halothane, the blood pressure returned to 150/110 torr; hydralazine and subsequently methyldopa were required to maintain diastolic pressure below 120 torr.

Microscopically, the mass proved to be a Wilms' tumor with capsular infiltration. Biopsied adjacent nodes were negative for tumor, as was a biopsy of the opposite kidney. Chemotherapy and radiotherapy were begun, and at the time of discharge, 21 days postoperatively, the patient required continuation of methyldopa for adequate control of his blood pressure.

At the most recent follow-up, 7 months after tumor removal, antihypertensive therapy was discontinued, as the blood pressure had gradually returned to normal.

DISCUSSION

Except in association with pheochromocytoma, no description of the anesthetic management of the severely hypertensive child can be found in pediatric anesthesia texts. In the case of pheochromocytoma, hypertension is generally controlled pharmacologically prior to operation, so that normal blood and ECF volumes can be restored. With a Wilms' tumor, however, no reliable method of preoperatively adjusting vasomotor tone or blood volume toward normal has been reported.

Presumed mechanisms for the hypertension associated with Wilms' tumor include elevated renin levels secondary to renal ischemia produced by mechanical compression of the renal artery, secretion of renin by the tumor itself, and a possible unidentified pressor substance secreted by the tumor.[2] However, none of these possibilities would fully explain the observed course in this patient; he remained hypertensive for several months postoperatively, as have 2 previously reported patients.[2,5] Causes for continued renin production or pressor substance secretion in our patient were not apparent; there was no demonstrable residual or metastatic tumor tissue and the contralateral kidney was normal. Elevated blood-renin levels were present intraoperatively, but these values fell to normal by the day after operation. In spite of normal renin levels, antihypertensive medication was still necessary for pressure control.

Problems may be posed by therapy aimed at lowering blood pressure preoperatively. In 2 reported instances,[3,7] attempted preoperative control with antihypertensive drugs has not been successful; both children died preoperatively of hypertension-related complications. Of added interest, if renin is indeed a factor in the production of hypertension with Wilms' tumor, acute diuretic administration and vasodilating antihypertensive drugs may further increase renin activity.[8] Propranolol has been recently reported to cause a fall in renin activity,[8] so that one might be presented preoperatively with a child acutely treated with propranolol. The consequences of acute and possibly intense beta-blockade just prior to anesthesia have not yet been fully demonstrated.

Aggressive diuretic therapy may also alter serum electrolytes significantly. In our patient, serum K^+ fell from 3.5 to 2.7 mEq/L preoperatively. Use of nondepolarizing muscle relaxants could, therefore, result in a neuromuscular block which could not be predictably antagonized. Dangerous ventricular arrhythmias could be produced by halothane anesthesia administered in face of hypokalemia and hypertension. In addition, the possibility of acute ECF depletion consequent to potent diuretics might be masked by a marked degree of systemic vasoconstriction. In that situation, precipitous falls in blood pressure from anesthetic-induced vasodilation and myocardial depression could be predicted.

Presented with a child with severe, uncontrolled hypertension, we chose halothane for its controllability in lowering blood pressure to the desired level. We were concerned that sustained systolic levels of 150 to 200 torr would contribute to massive blood loss during resection. Equally worrisome was the possibility of a cerebrovascular accident if a further increase in blood pressure ensued during manipulation of the tumor. The possibility of a catecholamine-secreting tumor also was considered, despite a single preoperative negative urine spot test for vanillylmandelic acid.

Pharmacologic preparation for treatment of sudden hypotension and/or hypertension during extirpation of the tumor seemed prudent. However, the ease with which the blood pressure was controlled intraoperatively in this child was a pleasant surprise; this finding is consonant with the experience of at least 1 other pediatric anesthesia group.*

REFERENCES

1. Bradley JE, Pincoffs MC: The association of adenomyosarcoma of the kidney (Wilms' tumor) with arterial hypertension. Ann Intern Med 11: 1613-1628, 1938

2. Ganguly A, Gribble J, Tune B, et al: Renin-secreting Wilms' tumor with severe hypertension. Ann Intern Med 79:835-837, 1973

3. Hughes JG, Rosenblum H, Horn LG: Hypertension in embryoma (Wilms' tumor). Pediatrics 3:201-207, 1949

4. Koons KM, Ruch MK: Hypertension in a 7-year-old girl with Wilms' tumor relieved by nephrectomy. JAMA 115:1097-1098, 1940

5. Mitchell JD, Baxter TJ, Blair-West JR, et al: Renin levels in nephroblastoma (Wilms' tumor). Arch Dis Child 45:376-384, 1970

6. Sukarochana K, Tolentino W, Kiesewetter WB: Wilms' tumor and hypertension. J Pediatr Surg 7:573-578, 1972

7. Gooding CA, Raslavicius PA: Arteriographic demonstration of perirenal hematoma and Wilms' tumor in a hypertensive child. Am J Roentgenol Radium Ther Nucl Med 93:467-472, 1965

8. Oparil S, Haber E: The renin-angiotensin system. N Engl J Med 291:389-401, 1974

*Marcy JH, Children's Hospital, Pittsburgh, Pennsylvania, personal communication, 1974.

Clinical Evaluation of Injectable Lorazepam as a Premedicant: The Effect on Recall

CASEY D. BLITT, MD*
W. CLAYTON PETTY, MD†
WILL A. WRIGHT, MD‡
BARBARA WRIGHT§
Tucson, Arizona‖

A double-blind comparison of lorazepam and placebo, lorazepam and pentobarbital, and a comparison of lorazepam IV drip versus lorazepam IV bolus as a premedicant showed this new agent to offer promise as a sedative premedicant. However, the potency of the drug demands caution, and its use for outpatient premedication is not recommended.

LORAZEPAM¶, a 1,4-benzodiazepine sedative, has been reported to have antianxiety and antirecall effects.[1,2] The purpose of this study was to evaluate the efficacy of lorazepam as a preanesthetic medication in producing lack of recall for specific events prior to and after anesthesia and operation.

METHODS

Adult patients (n=140) in ASA classes I and II, weighing between 45 and 90 kg, were studied; all gave written informed consent before entering the study. None were receiving monoamine oxidase inhibitors or had a known sensitivity to barbiturates or benzodiazepines. No other sedatives or psychotropic durgs were permitted during the study, but no restrictions were placed on the technic of anesthesia selected. Neurosurgery, open-heart surgery, and organ-transplant surgery were specifically excluded.

The study was carried out in 3 parts. In part I, 50 patients were studied in a double-blind controlled manner, to document the differences between lorazepam (4 mg) and placebo (propylene glycol vehicle) administered IV. Meperidine (50 mg) and atropine (0.6 mg) were given IM to all patients approximately 1 hour before injection of lorazepam or placebo. Fifteen minutes after injection, a memory card consisting of a large dollar bill was displayed to obtain the patient's verbal response.

Patients were visually and verbally oriented to events and objects from the time they were transported from their hospital room until induction of anesthesia. Blood samples were analyzed for plasma concentrations of lorazepam. Twenty-four hours postoperatively, the following questions were asked:

1. Do you remember anything on the way to the operating room? 2. Do you remember entering the operating room? 3. Do you remember being moved from the stretcher to the operating table? 4. Do you remember seeing the operating room surgical light?

¶Ativan®: Wyeth

*Assistant Professor, Department of Anesthesiology.
†Assistant Professor, Department of Anesthesiology.
‡Instructor, Department of Anesthesiology.
§Research Assistant, Department of Anesthesiology.
‖University of Arizona, Tucson, Arizona 85724.
Supported by a grant from Wyeth Laboratories.
Paper received: 10/22/75
Accepted for publication: 11/10/75

5. Do you remember being shown a card yesterday? (If the patient could not remember being shown the card, he was reminded that he had been, and was asked to pick it out of a composite of 8 different cards.) 6. Do you remember leaving the recovery room? 7. Do you remember the physician cleansing your skin for anesthesia? 8. Do you remember the physician sticking you with a small needle and asking you when you could feel the needle? 9. Do you remember the anesthesia mask being placed over your face? 10. Do you remember doubling up your knees in preparation for the anesthesia? 11. Do you remember the physician starting the IV? 12. Did the injection make you sleepy or drowsy? 13. Do you remember leaving your hospital room?

Part II of the study was a double-blind controlled study of 50 patients to determine the difference between lorazepam (4 mg) and pentobarbital (100 mg), administered IM as the sole premedicant the morning of operation. About 2 hours later, the memory card was shown. Patients were visually and verbally oriented to events and objects from the time they were transported from their hospital room until induction of anesthesia. The standard 24-hour interview was performed to determine the patient's recall ability.

In part III of the study, 40 patients were given lorazepam, either by IV drip or by an IV incremental bolus, 60 minutes after 50 mg of IM meperidine and 0.6 mg of IM atropine, to determine if some clinical evidence other than drowsiness would act as an endpoint for the drug administration. Patients were visually and verbally oriented to events and objects from the time they were transported from their hospital room until induction of anesthesia. Fifteen minutes after administration of lorazepam, a memory card was shown and a 24-hour interview to test recall ability was conducted.

Age, weight, and height differences in all groups were analyzed using a 1-way analysis of variance. Race proportions in all groups were compared by chi-square. Sex proportions, anesthetic agents, muscle relaxants, other intraoperative medication received, medication received in the recovery room, supplemental anesthetics, and surgical procedure classification were compared in all 3 groups by Fisher's exact test.

A subjective response by the patient and physician regarding sedation and patient acceptance (excellent, good, fair, not acceptable) was also elicited and subjected to chi-square testing in all 3 groups. The Fisher test was used to compare results of the 24-hour interview and to compare the incidence of adverse effects in all groups.

RESULTS

The drug groups (stratified by general and regional anesthesia types) were found to be homogeneous with respect to age, weight, height, sex, race, anesthetic agents, intraoperative muscle relaxants and other medication received, medication in the recovery room, supplemental anesthesia, and surgical procedures.

Group I: Lorazepam Versus Placebo (IV).—The sedative effect of lorazepam was observed by both the patient and the physician and was well accepted by the patient. These effects were not always evident in the placebo group. Recall for specific events as elicited by questions asked in the 24-hour interview is shown in table 1. In the lorazepam group, 85% of the patients tested and

TABLE 1
Recall for Specific Events—Lorazepam vs Placebo

Events	Patients failing to recall/patients tested*	
	Lorazepam (4 mg IV)	Placebo (IV)
Entering OR	16/20† (80%)	2/20 (10%)
Stretcher to OR table	18/20† (90%)	2/19 (11%)
OR surgical light	15/20† (75%)	0/20 (0%)
Anesthesia mask	11/12† (92%)	4/16 (25%)
Cleaning skin	6/7‡ (86%)	0/3 (0%)
Doubling up knees (regional anesthesia)	3/3 (100%)	0/3 (0%)
Needle for anesthesia level	6/7‡ (86%)	0/3 (0%)
Leaving recovery room	16/19† (84%)	7/20 (35%)

*Ten patients in a pilot study not included in statistical analysis.
†$p<0.01$.
‡$p<0.05$.
( ) Percent failure to recall.

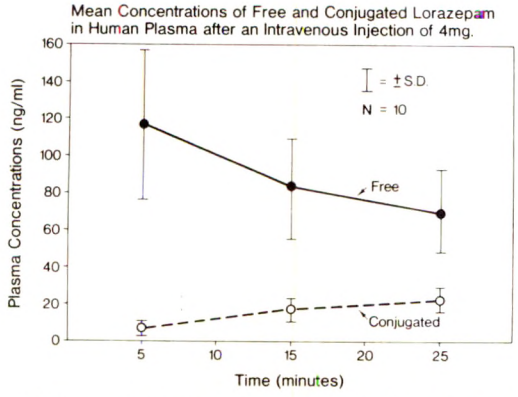


FIGURE. Concentrations of free and conjugated Lorazepam in human plasma after an intravenous injection of 4 mg.

5% of those tested in the placebo group ($p<0.01$) failed to recall the memory card, while 76.5% and 0% respectively, failed on the composite recognition aspect. Two patients given lorazepam who exhibited disorientation and hallucinatory behavior, responded satisfactorily to physostigmine.

The figure shows mean concentrations of free and conjugated lorazepam in human plasma following IV injection of 4 mg. No correlation appeared between plasma concentrations of lorazepam and lack of recall. Table 2 shows the relationship of the degree of sedation, recall, and recognition of the memory card in 10 patients.

Group II: Lorazepam Versus Pentobarbital (IM).—An immediate pain reaction at the injection site was experienced in significantly more of the patients receiving lorazepam ($p<0.01$). No significant difference was found in sedation between the 2

TABLE 2

Plasma Levels of Free Lorazepam (ng/ml) Obtained 15 Minutes After An IV Dose of 4 mg, and Their Relationship to the Degree of Sedation, Recall and Recognition of the Memory Card

Patient number	Plasma concentration (ng/ml)		Degree of sedation	Memory card	
	Free	Conjugated		Recall	Recognition
121	56.2	17.8	Marked sedation	(−)	(−)
124	90.3	12.2	Marked sedation	(−)	(−)
125	66.5	18.9	Marked sedation	(−)	(+)
127	122.9	27.4	Marked sedation	(−)	(+)
129	121.4	23.3	Marked sedation	(−)	(−)
133	99.5	21.9	Sedation	(−)	(−)
134	106.1	7.3	Marked sedation	(−)	(−)
136	99.3	11.6	Sedation	(−)	(+)
138	44.3	20.2	Marked sedation	(−)	(−)
140	46.0	11.2	Marked sedation	(−)	(−)

TABLE 3

Recall for Specific Events—Lorazepam vs Pentobarbital

Events	Patients failing to recall/patients tested	
	Lorazepam (4 mg IM)	Pentobarbital (100 mg IM)
Leaving hospital room	8/25* (32%)	0/25 (0%)
Anything on way to OR	14/25† (56%)	5/24 (21%)
Entering OR	14/25* (56%)	3/25 (12%)
Stretcher to OR table	18/25* (72%)	4/25 (16%)
Starting IV	11/24* (46%)	0/23 (0%)
OR surgical light	17/25* (68%)	3/25 (12%)
Anesthesia mask	14/19* (74%)	4/23 (17%)
Cleaning skin	2/7 (28%)	0/2 (0%)
Doubling up knees (regional anesthesia)	2/2 (100%)	—
Needle for anesthesia level	4/7 (57%)	0/2 (0%)
Leaving recovery room	19/25* (76%)	8/25 (32%)

*$p<0.01$.

†$p<0.05$.

( ) Percent failure to recall.

groups. ("Did the injection make you feel sleepy or drowsy?") No significant differences were noted regarding patient acceptance of medication or the physician's clinical judgment of premedication. Patients given lorazepam showed significantly less ability to recall events than those given pentobarbital, as evidenced by the results of the 24-hour interview (table 3). Sixty-eight percent of the patients in the lorazepam group could not recall the memory card and 47% failed to recognize the card from the composite picture. Only 16% in the pentobarbital versus 68% in the lorazepam group ($p<0.01$) failed to recall the card, and all recognized the card from the composite picture.

Part III: Lorazepam Drip Versus Bolus.—Drowsiness appeared at a mean dose of 0.053 (± SD 0.0268) mg/kg and at a mean time of 8.15 (± SD 3.4) minutes with the IV continuous drip method and with a mean dose of 0.059 (± SD 0.0268) mg/kg and a mean time of 6.9 (± SD 3.19) minutes by bolus. However, lack of ability to recall specific events was equally evident by both technics, as 82% could not recall the memory card and 64% failed to recognize the card from the composite picture. With sedation as an endpoint, 32/38 patients said they felt sleepy or drowsy following the injection. Euphoria was seen in 1 patient and hallucinations, with difficulty in depth perception, were reported by another. Acceptance of the medication by physicians and patients was good.

DISCUSSION

Our study indicates that lorazepam is a satisfactory preanesthetic sedative. Additionally, it effectively prevents recall of events surrounding the operative period, an effect certainly beneficial in some patients. The drug is well accepted and well tolerated by patients but is extremely potent and may prove difficult to learn to use effectively, since it is easy to "severely obtund" a patient for a long time in the postoperative period if too much is given. We recommend that it not be used for premedication of outpatients.

It became obvious at the end of our study that the dosage of lorazepam necessary to produce lack of recall may not necessarily correlate with the dosage necessary to produce an easily recognizable clinical effect, but the agent appears compatible with current anesthetic agents and technics. Although 3 patients exhibited CNS excitation following its administration, all were easily reversible with physostigmine.[3]

The benzodiazepine tranquilizer, diazepam, has been used successfully as an amnesic in combination with the N_2O-narcotic-muscle relaxant technic.[4,5] Ghoneim's group[6] attempted to relate plasma levels of diazepam and a diazepam metabolite, desmethyldiazepam, to mood levels. Correlation was found between plasma levels of diazepam and some of the mood ratings, but these authors concluded that plasma levels cannot be meaningfully related to cerebral effects without further studies. We have not seen any correlation between plasma levels of lorazepam and recall ability.

REFERENCES

1. Knapp RB, Fierro L: Evaluation of the cardiopulmonary safety and effects of lorazepam as a premedicant. Anesth & Analg 53:122-124, 1974

2. Heisterkamp DV, Cohen PJ: The effect of intravenous premedication with lorazepam (Ativan), pentobarbitone or diazepam on recall. Br J Anaesth 47:79-81, 1975

3. Blitt CD, Petty WC: Reversal of lorazepam delirium by physostigmine. Anesth & Analg 54:607-608, 1975

4. Fishburne JI Jr, Fulghum MS, Hulka JF, et al: General anesthesia for outpatient laparoscopy with an objective measure of recovery. Anesth & Analg 53:1-6, 1974

5. Eisenberg L, Taub HA, Burana A: Memory under diazepam-morphine neuroleptanesthesia in male surgical patients. Anesth & Analg 53:488-495, 1974

6. Ghoneim MM, Mewaldt SP, Ambre J: Plasma levels of diazepam and mood ratings. Anesth & Analg 54:173-177, 1975

Intraoperative Awakening for Early Recognition of Possible Neurologic Sequelae During Harrington-Rod Spinal Fusion

K. G. SUDHIR, FFARCS*
ROBERT M. SMITH, MD†
JOHN E. HALL, MD‡
DOLLY D. HANSEN, MD§
Boston, Massachusetts‖

To permit early recognition of possible cord trauma due to spinal fusion with Harrington-rod instrumentation, 42 patients were awakened intraoperatively for testing voluntary motor function of the limbs. N_2O-O_2-curare and morphine were used for anesthesia in all patients. In 5 patients, who refused IV induction, halothane was given for induction only. Only 1 patient had any complaint referrable to being awakened intraoperatively. The awakening caused no displacement of Harrington rods in any patient. No neurologic sequelae were found.

POSTERIOR spinal fusion with Harrington-rod instrumentation for correction of scoliosis is increasingly common. One of the complications of this operation is paraplegia, with a reported incidence of 0.1%.[1]

To prevent this complication, Vauzelle and associates[2] awakened patients intraoperatively to check voluntary motor power of the limbs. The anesthetic agents used were hydroxydione, sodium succinate, succinylcholine, and diallylnortoxiferine (Alcuronium®) plus a narcotic (unnamed). Intraoperative check disclosed loss of voluntary leg motion following rod placement in 3 patients. In the first, motion returned within 5 minutes of rod removal. When the rod was replaced with less distraction, voluntary leg motion was lost again, but was regained on rod removal. In the second, the authors were able to replace the rod later, after halo traction. In the third, reduction of the distraction was sufficient to bring about return of function without removal of the rod.

At the Children's Hospital Medical Center of Boston, 340 patients were operated on for spinal fusion during the year October 1974-September 1975. Of this series, 2 patients are known to have had postoperative neurologic deficits. The loss of motor function in one was related to spinal operation but not to Harrington-rod instrumentation. The second case is reported here as an example of transient neurologic deficit due to use of a Harrington rod; this was detected early and countermeasures were taken which prevented permanent neurologic damage. The anesthetic technic employed for patients to be awakened intraoperatively is also described.

CASE REPORT

A 15-year-old girl was admitted with a diagnosis of idiopathic scoliosis which had been detected during a routine physical examination. She had no cardiorespiratory symptoms attributable to scoliosis. Neurologic findings were benign. Standing roentgenograms showed a right thoracic curve of 57° from 6th dorsal to 1st lumbar vertebras and a left lumbar curve of 43° from 1st lumbar to 5th lumbar vertebras. Hematocrit was 43.3% and urinalysis, electrolytes,

*Staff Anesthesiologist, Children's Hospital Medical Center.
†Chief Anesthesiologist, Children's Hospital Medical Center.
‡Professor of Orthopaedics, Harvard Medical School, Chief of Orthopaedic Surgery, Children's Hospital Medical Center.
§Staff Anesthesiologist, Children's Hospital Medical Center.
‖Departments of Anesthesiology and Orthopaedics, Children's Hospital Medical Center, Boston, MA 02115.
Paper received: 11/14/75
Accepted for publication: 12/3/75

prothrombin time, and partial thromboplastin time were normal. Chest x-ray and pulmonary-function tests showed moderate restrictive lung disease.

The patient was scheduled for posterior spinal fusion from 5th dorsal to 3rd lumbar vertebras with iliac bone graft and Harrington-rod instrumentation. Premedication consisted of pentobarbital, 2 mg/kg orally at 0500 hr, and atropine (0.015 mg/kg), and morphine (0.15 mg/kg) IM, 90 minutes before operation , which was at 0800 hr. Anesthesia was induced with thiopental (5 mg/kg) and succinylcholine (1.5 mg/kg) IV, followed by endotracheal intubation with a 7-mm cuffed tube. Anesthesia was maintained with N_2O-O_2-curare and morphine. Anesthetic course throughout the operation was uneventful.

At the end of the procedure, the patient was turned supine on a Striker frame, with the endotracheal tube in place. Muscle relaxants were reversed with atropine and neostigmine. The N_2O was discontinued and 100% O_2 was administered. The patient opened her eyes and was awake within a few minutes.

As the anesthesiologist was preparing to extubate the patient, one of the surgeons asked the patient to move her feet. She was able to move her right foot but not her left. A sensory deficit was noted on the right side up to the midthoracic level. The patient also had urinary incontinence. At this time, she was conscious enough to raise her head, both arms, and right foot, but still could not move her left foot.

With the patient reanesthetized and placed prone on the operating table, the surgical incision was reopened and the Harrington rod removed. Fifth dorsal to 3rd lumbar interspaces were explored, but no abnormality could be detected. The incision was closed and the patient was again awakened in the supine position, but was still unable to move her left foot. Immediate postoperative neurologic examination demonstrated a band of sensory loss below the left nipple, loss of motor function in the left lower limb, and sensory loss in the right lower limb.

Progressive neurologic improvement was noted over the next 12 hours. A myelogram on the 1st postoperative day was negative. The patient remained incontinent of urine for the next 8 days and required intermittent catheterization (12 hourly). On the 9th postoperative day, urinary residual increased, and a cystometrogram showed a hypotonic autonomous bladder with denervation hypersensitivity to bethanechol chloride (Urecholine®). Intermittent catheterization was continued.

Treatment by localizer cast reduced her dorsal curve to 37° and lumbar curve to 23°. She was discharged to recumbency at home on the 23rd postoperative day. At followup 3 months later, a repeat cystometrogram was normal and the patient was found to have complete motor and sensory recovery except for a patch of sensory loss on the left side of the chest.

CASE DISCUSSION

The most likely cause of neurologic deficit after Harrington-rod instrumentation is the stretching of the arteries supplying the spinal cord. It is known that transient spasm or prolonged occlusion of the artery of Adamkiewicz will cause paraplegia at the 8th dorsal level.[3] Most paraplegias resulting from correction of scoliosis are at the 8th dorsal level, in curves measuring over 100°.[4] Other causes could be accidental surgical trauma to the spinal cord or compression of the spinal cord due to hematoma formation. In this patient, exploration of the wound did not reveal any visible damage to the cord, and the postoperative myelogram ruled out hematoma. Neurologic improvement during the 24 hours postoperatively indicated that the trauma to the spinal cord was of a transient nature.

Awakening Technic.—To prevent recurrence of the above complication, the practice of awakening patients during Harrington-rod instrumentation was adopted at Children's Hospital Medical Center and applied to 42/46 patients between January and May 1975. Of the 4 patients not awakened, 2 were mentally retarded and 2 were considered too young to cooperate (1 and 3 years of age). Preoperatively, all parents and all older children and adults were informed of this procedure, but younger children, under age 12, who might be frightened, were not so informed.

Preoperative medication for all patients consisted of pentobarbital (2 to 4 mg orally on the morning of operation) and atropine (0.015 mg/kg) with morphine sulfate (0.1 mg/kg IM) 90 minutes before operation. In 41/46 patients, anesthesia was induced by IV thiopental (3 to 5 mg/kg) followed by

1 mg/kg of succinylcholine and tracheal intubation. Five patients who refused IV injection were induced with N_2O-O_2-halothane. The halothane was used only for induction and was discontinued after an IV infusion was established. Anesthesia was maintained with N_2O-O_2-curare and morphine in all patients. Dosage of morphine during the operation varied from 0.1 to 0.2 mg/kg and curare from 0.35 to 0.5 mg/kg initially, with supplemental doses of 0.01 to 0.05 mg/kg morphine and 0.1 to 0.3 mg/kg curare, when necessary.

No special attempt was made to keep patients under light anesthesia for the sake of intraoperative awakening. Intervals from the induction of anesthesia to intraoperative awakening varied from 2½ to 6 hours and intervals from the last dose of curare to the time of intraoperative awakening ranged from 10 minutes to 4 hours.

To test spinal function after the Harrington rods were in place, N_2O was discontinued and patients were hand-ventilated with O_2. At this time, we insisted that the operative procedure be stopped and silence be maintained in the operating room while patients were awakened and until they were reanesthetized. A member of the anesthesia team observed the patient's feet under the drapes. Within 1 minute, the anesthesiologist called the patient by name and asked him to move his hands and feet. The *maximum time* to awaken after the N_2O was turned off was 5 minutes, and in most patients was less than 2 minutes.

Increases in blood pressure of 10 to 20 torr and pulse rate of 10 to 20/minute were noted in all patients at this time. In 1 patient, the curare had to be reversed with atropine and neostigmine before the patient was able to move his hands and feet on command. His last dose of curare had been given 20 minutes prior to intraoperative awakening. In 1 other patient, naloxone hydrochloride was needed to reverse the morphine. As soon as movement of the hands and feet was noted, patients were reanesthetized with 70% N_2O and 30% O_2, followed by thiopental (1 to 2 mg/kg) and supplemental doses of curare and morphine. Diazepam (0.1 mg/kg) was given to provide retrograde amnesia.[5]

In most instances, curarization was reversed and patients extubated in the operating room. In patients whose preoperative pulmonary-function tests showed less than 50% of predicted value, curare reversal has not been attempted. These patients have been supported by mechanical ventilation for 24 hours after operation, then weaned by intermittent mandatory ventilation and extubated when their vital capacity was more than 10 to 15 ml/kg and their inspiratory force more than 25 to 30 cm H_2O. In postoperative interviews, 41/42 patients who were awakened intraoperatively did not have any complaints related to anesthesia.

No leading questions were asked regarding intraoperative awakening, and in only 1 patient was there any recollection of the event. This patient, a 30-year-old woman who previously had required tranquilizer therapy, complained that she remembered hearing the surgeons talking about her during the operation. She recalled music being played in the operating room and could also feel the surgeons working on her back, stating that she did not feel pain but complaining that it was unpleasant. She had undergone a posterior spinal release 2 weeks before the Harrington-rod fusion and had required high doses of morphine for pain postoperatively. During the operation for spinal release, no difficulty was encountered during anesthesia, but during the operation for Harrington-rod fusion, she required more frequent and higher doses of morphine and curare than during the preceding operation, possibly through development of acute tolerance to opiates.

In no patient in whom this technic was used were there any neurologic sequelae. This does not mean that there might not be in the future, but it does offer a means of early recognition and treatment. Awakening and movement of patients intraoperatively did not dislodge the Harrington rod in any patient.

REFERENCES

1. Harrington PR: Instrumentation techniques in spine surgery. The 3rd Annual Postgraduate Course on the Management and Care of the Scoliotic Patient. New York Orthopedic Hospital of the Columbia-Presbyterian Medical Center, December 2-4, 1971

2. Vauzelle C, Stagnara P, Jouvinroux P: Functional monitoring of spinal cord activity during spinal surgery. Clin Orthop 93:173-178, 1973

3. Keim MA: Blood supply to the spinal cord. The 2nd Annual Postgraduate Course on the Management and Care of the Scoliotic Patient. New York Orthopedic Hospital of the Columbia-Presbyterian Medical Center, November 5-6, 1970

4. Harrington PR: Instrumentation techniques in spine surgery. Orthop Clin North Am 3:49-67, 1972

5. Dundee JW, Keilty SR: Diazepam. Int Anesthesiol Clin 7:91-121, 1969

Fluroxene (2, 2, 2-Trifluoroethyl Vinyl Ether) Toxicity: A Chemical Aspect

G. G. HARRISON, MD, FFARCS*
K. IVANETICH, PhD†
L. KAMINSKY, PHD‡
M. J. HALSEY, D PHIL§

Fluroxene is highly toxic to several animal species. This toxicity is enhanced by induction of raised levels of hepatic microsomal enzymes. Experiments in rats are described which seek to assess the relative contribution to this toxicity of the individual component groups of the fluroxene molecule. Though results point to the trifluoroethyl moiety of fluroxene as that aspect of the molecule most responsible for the observed mortality, reduction of the vinyl group modifies the pattern of liver injury. That the liver necrosis, manifest following fluroxene anesthesia in the presence of microsomal induction, is alone the direct cause of the acute death of experimental animals is questioned.

THE anesthetic, fluroxene, has recently been demonstrated to be toxic to several animal species under certain circumstances.[1] Rats, guinea pigs, and mice have been shown to display toxic effects when chronically exposed to concentrations of fluroxene as low as 30 parts per million (1/2000 MAC).

That this toxicity is the result of some aspect of fluroxene biotransformation, rather than an effect of fluroxene itself, is suggested by the demonstration of increased manifestations of toxicity following hepatic microsomal enzyme induction, with a decrease in these when microsomal enzyme activity is suppressed.[2,3]

There is some evidence to suggest that formation of the highly toxic trifluoroethanol from the fluorinated ethyl moiety of fluroxene is responsible for these toxic effects.[4,5] But, whereas fluroxene anesthesia in the presence of enhanced hepatic microsomal mixed function oxidase levels resulted in florid liver necrosis,[6] direct exposure of animals to trifluoroethanol resulted in the death of the animal without similar histologic changes in the liver.[5] We questioned, therefore, the contribution to the manifest toxicity that might result from the catabolism of the vinyl moiety of fluroxene.

To this end, we exposed groups of rats in

*Associate Professor, Department of Anaesthetics, University of Cape Town.

†Senior Lecturer, Medical Biochemistry, Department of Physiology, University of Cape Town.

‡Senior Lecturer, Medical Biochemistry, Department of Physiology, University of Cape Town.

§Senior Research Scientist, Division of Anaesthesia, Clinical Research Centre, Northwick Park, England.

Departments of Anaesthetics and Medical Biochemistry of the University of Cape Town, South Africa, and the Division of Anaesthetics, Clinical Research Centre, Northwick Park, Harrow, England.

This study was supported in part by grants from the Anglo American and De Beers Anaesthetic Research Fund, the South African Medical Research Council, and the University of Cape Town Staff Research Fund.

Paper received: 9/17/75
Accepted for publication: 12/3/75

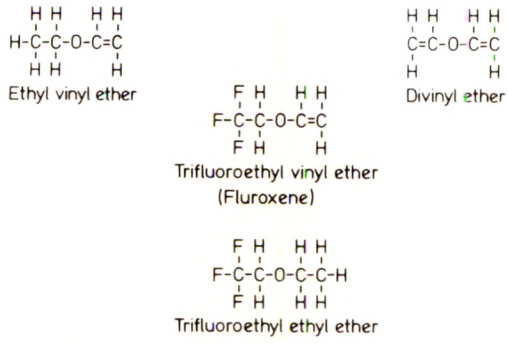


FIG 1. Structural formulas of fluroxene and the 3 related compounds studied.

which levels of microsomal enzymes had been increased (together with appropriate control groups) to fluroxene anesthesia and to 3 related compounds, each of which comprised some aspect of the fluroxene structure. We noted thereafter manifestations of toxicity as determined by (1) death or survival of the animal and (2) examination of liver histology.

The structural formulas of fluroxene and the 3 other anesthetic compounds exemplifying modifications of aspects of this structure (fig 1) are as follows:

1. Fluroxene: 2,2,2-trifluoroethyl vinyl ether.*

2. Vinamar, or ethyl vinyl ether, the nonfluorinated analog of fluroxene.†[7]

3. Vinesthene, or divinyl ether.‡[8]

4. Trifluoroethyl ethyl ether (TFEE), a chemically reduced form of fluroxene in which the vinyl moiety is hydrogenated to an ethyl group.

METHODS

The experimental animals were 200 to 300-gm male Sprague Dawley rats. Liver microsomal enzyme levels were enhanced by the daily intraperitoneal administration of phenobarbital (80 mg/kg/day) for 3 days preanesthetic. The concentration of phenobarbital sodium in saline solution used was 10 mg/ml, giving injection volumes of approximately 2 ml. Control rats were injected with similar volumes of physiologic saline solutions.

Having been allowed food and water ad lib until then, rats were starved for 24 hours after the 3rd phenobarbital injection, at which time (day 4) they were anesthetized. In the event of survival, this program was repeated. Survivors were then sacrificed by cervical dislocation on the 3rd day thereafter.

Animals were anesthetized in groups of 5 for periods of 3 hours in a standard dessicator 28 cm in diameter with a volume of 27.3 L, of which 4 L, the volume below the grid, was filled with standard anesthetic soda lime. Additional chemical CO_2 absorption was provided for by the placement of extra vertically standing perforated containers of soda lime between the animals.

The anesthetic agents were carried by a flow of O_2 (5 L/min) passed through a vaporizer and the anesthetic chamber in series. In such circumstances, the level of ambient CO_2 in the anesthetic chamber was less than 1%. In the case of ethyl vinyl ether and divinyl ether, because of their limited availability, a lower O_2 flow (2 L/min) was used.

Animals were exposed to anesthetic and subanesthetic concentrations of fluroxene (3 and 0.5%) delivered from a Fluoromartec® vaporizer, or to concentrations of the other agents sufficient to maintain a very light level of anesthesia, in equianesthetic concentrations. This level of anesthesia was defined as that at which response to paw-pinching became obtunded. TFEE, which produced anesthesia in rats, was synthesized in our laboratory by reduction of commercially available fluroxene with hydrogen in the presence of a palladium catalyst. Reduction of the vinyl function was checked by IR spectrophotometry, the material being treated to remove peroxides and redistilled before use.[9] All agents were screened to exclude the presence of peroxides.

After the death or sacrifice of experimental animals, the livers were immediately excised and fixed in formalin. Thereafter, sections of liver were stained with hematoxylin-eosin (H & E) and submitted to light microscopy.

RESULTS

The tabulated results, in terms of anesthetic agent, number of 3-hour exposures, mortality, and histology (table) reveal that all enzyme-induced rats exposed to fluroxene, both in anesthetic and subanesthetic concentrations, died after a single 3-hour exposure. Similar mortality followed expo-

*Ohio Medical Products.
†Fluka, AG.
‡British drug houses.

TABLE

Anesthetic	Microsomal state: + = with induction 0 = no induction	Duration of anesthetic, hours	Number of exposures	Mortality	Histology
Fluroxene 3%	+	3	1	20/20	Periportal congestion, gross centrizonal necrosis or marked cell damage in all.
0.5%	+	3	1	10/10	Periportal congestion, gross centrizonal necrosis or marked cell damage in all.
3%	0	3	2	0/20	Periportal hydropic changes, 8/20.
0.5%	0	3	2	0/10	Normal histology.
TFEE	+	3	1	12/12	Frank centrizonal necrosis, 2/12. Marked fatty infiltration ± areas of focal necrosis and cell damage, 10/12
	0	3	1	0/12	No centrizonal necrosis. Miliary fatty infiltration and periportal hydropic degeneration, 6/12.
Vinamar	+	3	2	0/9	No necrosis. Periportal hydropic degeneration, 2/9.
	0	3	2	0/10	No necrosis. Periportal hydropic degeneration, 5/10.
Vinesthene	+	3	2	0/5	No necrosis. Periportal hydropic degeneration, 4/5.
	0	3	2	0/5	No necrosis. Periportal hydropic degeneration, 4/5.

sure of enzyme-induced rats to TFEE. This mortality, which occurred during or shortly after anesthesia, was associated with histologic evidence of severe centrizonal liver damage: frank necrosis, chromatolysis, fatty infiltration, pyknosis, and cloudy swelling (figs 2 and 3). Congestion, especially in the periportal areas, was a marked feature, particularly of those enzyme-induced animals anesthetized by fluroxene. The incidence of frank necrosis was much lower in enzyme-induced animals after anesthesia with TFEE, in which circumstance marked fatty infiltration with centrizonal pallor was the most consistent finding (fig 4). The magnitude of histologic liver damage in some animals after TFEE did not appear sufficient to account for death.

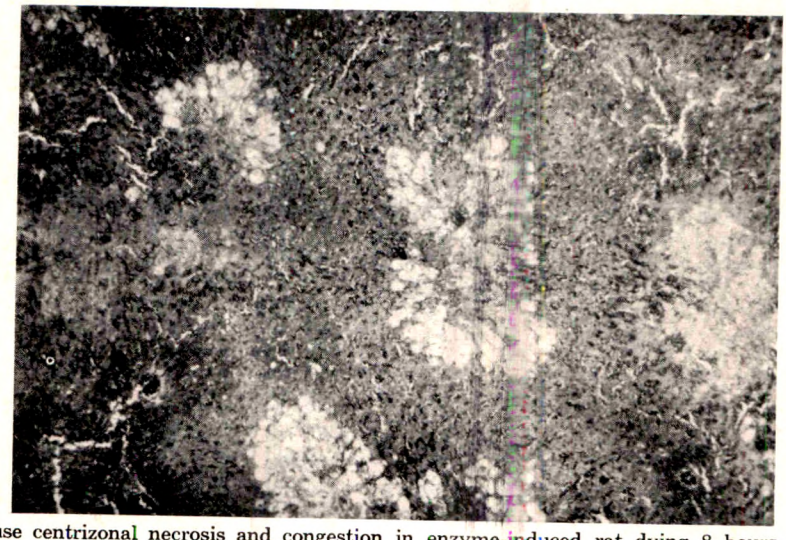


FIG 2. Diffuse centrizonal necrosis and congestion in enzyme-induced rat dying 8 hours after 3-hour exposure to 0.5% fluroxene. H & E x 160.

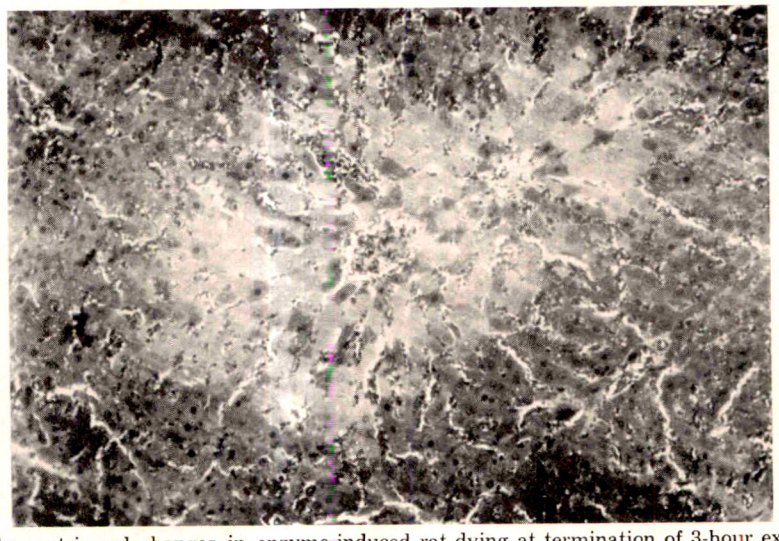


FIG 3. Early centrizonal changes in enzyme-induced rat dying at termination of 3-hour exposure to 3% fluroxene. Note chromatolysis, pallor, congestion, and occasional pyknotic cells. H & E x 400.

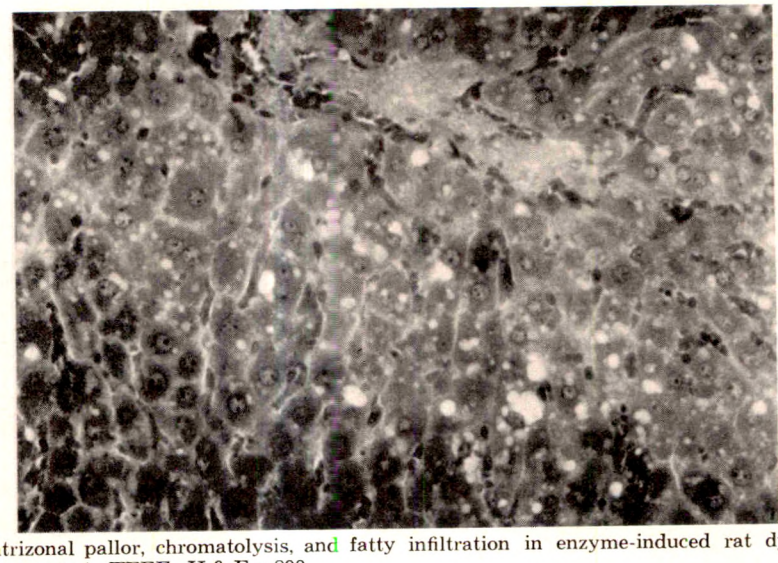


FIG 4. Centrizonal pallor, chromatolysis, and fatty infiltration in enzyme-induced rat dying 12 hours after 3-hour exposure to TFEE. H & E x 800.

No mortality occurred in the relevant fluroxene- or TFEE-anesthetized, uninduced controls, nor in any induced or uninduced animal exposed to vinamar or vinesthene. Nor was there evidence of centrizonal necrosis in any of these animals. However, the livers of some showed a nonspecific periportal hydropic change, apparent in both enzyme-induced and uninduced control animals.

DISCUSSION

Following phenobarbital induction of microsomal enzymes—

1. Fluroxene, even in subanesthetic concentrations, causes florid liver necrosis and death.

2. Modification of the vinyl group of fluroxene to an ethyl moiety does not lessen this mortality, though it does produce a different and less extreme pattern of liver damage.

3. Neither mortality nor histologic liver necrosis followed repeated exposures of animals to ethyl vinyl ether or divinyl ether.

Considering as the index of toxicity the mortality which occurred in the presence of enzyme induction following exposure of rats

to the test agents, it is immediately apparent that the trifluoroethyl moiety is the common denominator, no mortality resulting in its absence. However, the modification of the histologic pattern of liver injury following the use of TFEE rather than fluroxene suggests that the vinyl group must in some way be involved in the induction of the liver damage which, in itself therefore, may not be the direct cause of death in the experimental animals. This is in agreement with our earlier report that catabolism of the vinyl group of fluroxene, *in vivo* or *in vitro*, results in the destruction of hepatic cytochrome P450.[3,9] It is surprising, in view of the apparent damage caused to the liver by the biotransformation of the vinyl group in fluroxene, that neither ethyl vinyl ether nor divinyl ether produces similar liver damage. This aspect is presently under investigation.

ACKNOWLEDGMENT

Liver sections in this study were cut by Mr. Stan Abbott of the Department of Surgery, University of Cape Town, South Africa, and Mr. Christopher Sowter of the Department of Pathology, Clinical Research Centre, Northwick Park, Harrow, England. Technical laboratory assistance was provided by Mrs. I. Zietsman and Mr. Brian Sasman of the Department of Anaesthetics, University of Cape Town, and Mr. Peter Bateman of the Department of Anaesthetics, Clinical Research Centre. To these we express our thanks.

REFERENCES

1. Stevens WC, Gibbons RT: Fluroxene toxicity in several species (abstract). San Francisco, American Society of Anesthesiologists Meeting, 1973, pp 185-186

2. Cascorbi HF, Singh-Amaranath AV: Fluroxene toxicity in mice. Anesthesiology 37:480-482, 1972

3. Ivanetich KM, Bradshaw JJ, Marsh JA, et al: The rôle of cytochrome P450 in the toxicity of fluroxene anesthesia in vivo. Biochem Pharmacol (in press)

4. Blake DA, Rozman RD, Cascorbi HF, et al: Biotransformation of fluroxene. Biochem Pharmacol 16:1237-1248, 1967

5. Blake DA, Cascorbi HF, Rozman RS, et al: Animal toxicity of 2,2,2-trifluoroethanol. Toxicol Appl Pharmacol 15:83-91, 1969

6. Harrison GG, Smith JS: Massive lethal hepatic necrosis in rats anesthetized with fluroxene after microsomal enzyme induction. Anesthesiology 39:619-625, 1973

7. Kranz JC, Carr CJ, Musser RD, et al: The anesthetic action of ethyl vinyl ether. J Pharmacol Exp Ther 90:88-93, 1947

8. Gelfan S, Bell IR: The anesthetic action of divinyl oxide on humans. J Pharmacol Exp Ther 47:1-3, 1933

9. Ivanetich KM, Marsh JA, Bradshaw JJ, et al: Fluroxene mediated destruction of cytochrome P450 in vitro. Biochem Pharmacol 24:1933-1936, 1975

Editors share the belief that medical writing is capable of vast improvement. This article is one of a series of personal communications from Charles G. Roland, M.D., former Senior Editor of JAMA, to John T. Martin, M.D., Associate Editor of Anesthesia & Analgesia . . . Current Researches. Dr. Roland is Chairman, Department of Biomedical Communications, Mayo Clinic, Rochester, Minnesota 55901.

Thoughts About Medical Writing

XXXVI. Writing an Editorial

Dear Tom:

Some time back I wrote about the case report and the letter-to-the-editor. So now, I thought I might write about that powerful medium, the editorial.

We need more editorials, and more effective editorials, in our journals. Through editorials we can disseminate informed opinion without immobilizing it in the plaster cast of the conventional medical article with its fixed format and rigid demand for statistical significance and controls.

You don't have to be an editor to write an editorial. Journals often request editorials from authors outside their staff. Moreover, the old idea that an editorial must express the official viewpoint of the editorial board or of the society or association that owns the journal has largely disappeared. Consequently, the editorial "we" is becoming archaic. Most often, editorials clearly express the opinions or sentiments of one person; and most often, editorials now are signed.

I believe that identifying the author of an editorial advances the cause of responsible medical journalism. But that policy puts extra pressure on the author because he or she cannot use anonymity as a shield. And you should keep this fact in mind; if you write an editorial and you are challenged, you may find opinion harder to defend convincingly than you would dry but verifiable fact.

What is a medical editorial? It is a brief article—typically 400 to 1,000 words—that expresses opinion or interprets the facts or opinions of others; the subject matter can be any aspect of medicine (or of any related subject approved by the journal's editor). A former colleague of mine once said that an editorial was whatever an editor wrote for the editorial page. Adding the clause "or asked to have written" would satisfy me.

Suppose an editor asks you to write an editorial but doesn't specify the topic. What should you write about? Davidson[1] identified 10 "tangential items" that would lead to suitable editorial themes; I have taken his list, revised and reworded it, and added the 11th item, which I believe is one of the commonest sources of editorial ideas.

1. Historical material
2. Public relations
3. Legislation and governmental activities
4. Economic considerations
5. Ethics and morality
6. Professional organizational matters
7. Relations with related groups
8. Semantic and terminologic problems
9. Philosophic excursions
10. Research and training
11. Critical commentary on scientific articles or books

You probably can supplement this list, but it makes a suitable starting point. Using the list, plus your daily newspaper or the latest issue of this journal, you should have no difficulty creating a substantial list of potential topics for editorials.

An invitation to write an editorial carries with it the opportunity to write more imaginatively and creatively than you can when writing a journal article. Certainly, you should try. The opportunity to use metaphor, humor, and other rhetorical devices awaits you. But remember not to overdo it. Ration yourself to one metaphor per editorial. Don't bore your reader with humor by straining too hard.

As is true for most kinds of nonfiction writing, editorial writing can be improved by studying the work of the experts. The journals I would recommend are the *Annals of Internal Medicine*, the *New England Journal of Medicine*, and *JAMA*—but remember that not everything you find there will be top quality; that would be expecting too much. You must read selectively. Singling out particular editorial writers carries even more danger, although the editors-in-chief of the first two journals I mentioned regularly achieve a high level. I identified a few others in an anthology that appeared a few years ago.[2]

You should be able to state the message of your editorial in one sentence. Indeed, I believe that you should *make* yourself do that before you actually begin writing the editorial. Once you have that statement in hand, the editorial itself should present a reasoned and logical argument to persuade your readers to accept your view or, at least, to acknowledge its plausibility.

Please remember the special importance of the opening sentence.[3] Your first sentence plays an enormous, if immeasurable, role in convincing your reader that he needs to take the time to read what you have written. Consider these opening sentences:

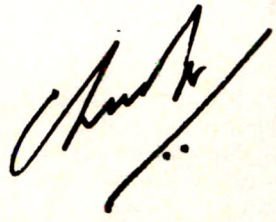
"Perhaps the most important sequel to the Arab oil embargo has been movement toward widespread adoption of nuclear energy."[4] (This plain but direct and effective sentence began an editorial on the recent rush to produce nuclear energy.)

"We live in a 'mammoriented' world."[5] (In this editorial, the writer discussed the FDA control of silicone materials proposed for use in augmenting the size of the female breast.)

"A little over a year ago my Aunt Martha died, but under the circumstances no one sent any flowers."[6] (This essay dealt with the burgeoning number of life-support devices available and the questions their use introduces about life and death.)

Your critical reading will reveal many additional examples. Once you can epitomize the gist of your editorial message in a thematic sentence, and once you have written an interesting, attention-gaining opening sentence, you are a long way toward preparing a good editorial. Now let's hope some editor has the good sense to invite you to write it.

Regards,



[Charles G. Roland, M.D.]

REFERENCES

1. Davidson HA: Guide to Medical Writing: A Practical Manual for Physicians, Dentists, Nurses, Pharmacists. New York, Ronald Press Company, 1957, p 251

2. Roland CG: Good Scientific Writing: An Anthology. Chicago, American Medical Association, 1971

3. King LS: The opening sentence. JAMA 202: 535-536, 1967

4. Abelson PH: A global rush toward nuclear energy (editorial). Science 191:901, 1976

5. Editorial: Abreast of the times. JAMA 195: 863, 1966

6. Barnes AC: RIP. Obstet Gynecol 26:599-600, 1965

Electroanesthesia (EA) Studies: EA Produced By Stimulation of Sensory Nerves of the Scalp in Rhesus Monkeys

TATSUHIKO KANO, MD*
GEORGE S. M. COWAN, MB, ChB†
ROBERT H. SMITH, MD‡
San Francisco, California§

After it was learned that electroanesthesia (EA) could not be produced in a Rhesus monkey which had undergone a circumferential scalp block with 0.25% lidocaine, it was postulated that EA could be produced by electrostimulation of the sensory nerves of the scalp in the rhesus. The work reported here verifies that EA can be produced by this method in this species; it is not necessary to pass current through the head.

WE HAVE been engaged in a continuing inquiry into the possibility of producing a state of clinical anesthesia solely by the application of electric currents, without supplementary drugs.[1-9] Our objective has been to get adequate current into the thalamus and to so overstimulate it as to prevent transmission of "pain-impulses" through the area.[3,9] Pathways for current were studied, and the most effective, in terms of minimal current requirements, was found to be between the orbits and the foramen magnum.[3]

Studies on blind human subjects, in whom the pathway between the orbits and foramen magnum was used, revealed that electrostimulation of the maxillary branch of the trigeminal nerve in the orbit produced aching in the maxillary teeth when over 30 ma was applied. In monkeys, that current magnitude is not required and we have seen no evidence of toothache in this species, so we have continued the use of the pathway between the orbit and the foramen magnum.

In the course of animal studies using this pathway, we discovered that a monkey could not be anesthetized by current after a circumferential scalp block was effected with 0.25% lidocaine without epinephrine.[1] This finding suggested that we might produce EA by electrostimulation of the sensory nerves of the scalp in monkeys.

The present study was designed to ascertain: (1) whether simple electrostimulation of the scalp overlying sensory nerves would produce EA, (2) how many of such scalp areas had to be stimulated, and (3) if electrostimulation of the posterior 2/3 of the scalp alone would produce EA. This seemed to us to be a possible means of producing EA without using the orbit-foramen magnum route and, in doing so, to eliminate risk to the eyes and stimulation of the V-2 nerves in the orbit.

METHOD

Twenty-five tests were made on 5 adult

*Anesthesiologist, Kumumoto Medical School, Kumumoto, Japan.
†Department of Surgery, Eisenhower Army Hospital, Fort Gordon, Georgia.
‡Professor Emeritus, University of California, San Francisco, California.
§Department of Anesthesia, University of California, San Francisco, California 94343.

This study was supported in part by US Army Contract DADA 17-71-C-1100.

Reprint requests to: Dr. Smith, Route 5, Box 1020, Hood River, Oregon 97031.

Paper received: 2/12/75
Accepted for publication: 12/16/75

Rhesus monkeys over a 1-month period. The animals were restrained in a chair so devised as to leave the head, hands, legs, and tail accessible. Each animal had a nasotracheal catheter in place during each test. (This measure is necessary because the restrained Rhesus will hold its breath when current is applied; the nasotracheal tube permits ventilation of the animal with air for a few breaths, to break the pattern of breath-holding.)

The patterns of electrode placement are depicted in figures 1 and 2. The current was applied between electrodes straddling specific nerves: the greater occipitals, the supraorbitals, and the greater auriculars.

The electrodes were subcutaneous safety pins or 2.5 cm diameter agar-saturated sponges. The distance between electrodes varied from 2 to 5 cm. No local anesthetic was used in the placement of subcutaneous electrodes. The usual pattern was the insertion of an 18-gauge needle through the skin into the subcutaneous tissue, then bringing the tip out through the skin 2.5 cm lower. The safety pin, with its tip in the needle lumen, followed the needle as it was withdrawn. Safety pin electrodes were sterile #1 standard stainless-steel, with the pin portion coated with a dielectric substance except for 1 cm in the center; there was no bare metal against the skin. Sponge electrodes were applied in plastic electrode holders taped in place.

The anterior pair of electrodes, which straddled the supraorbital nerve, was used in the first part of the study but was omitted when it was learned that it was not needed. The current form was bidirectional square pulse. The duty cycle (percentage of pulse duration that current is flowing) was kept in the 20 to 40% range. The generators are so constructed as to produce a bidirectional square pulse. Frequency range is 100 Hz to 200 kHz. Duty cycle ranges from less than 1 to 50%. Peak current limit is 500 ma and is constant for a given average current; at a given average current meter reading, changing the duty cycle will change the average current leaving the peak current constant.

Basic frequency ranges were from 500 to 10,000 Hz. There were no mixtures of high (10,000 Hz) and low (500 Hz) frequencies

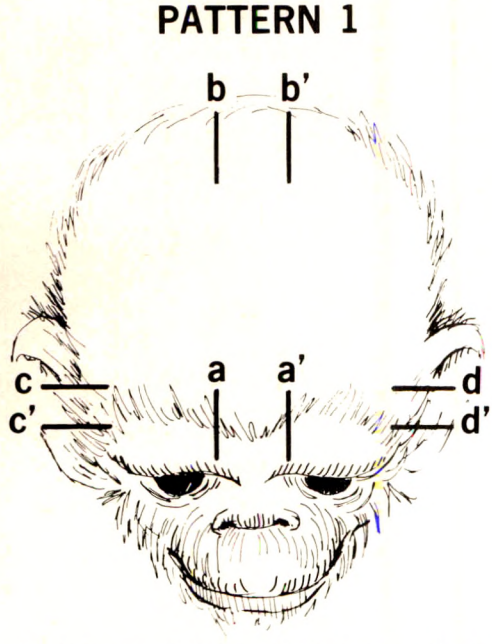


FIG 1. Pattern I. Using subcutaneous needle electrodes, the electrodes a and a′ straddle the main trunks of the 2 supraorbital nerves; b-b′ straddle the c-2-3 greater occipital nerves; c-c′ and d-d′ straddle the right and left greater auricular nerves, respectively. Milliamperage figures are average current; 20% duty cycle produces a peak current 5 times higher than the average current value.

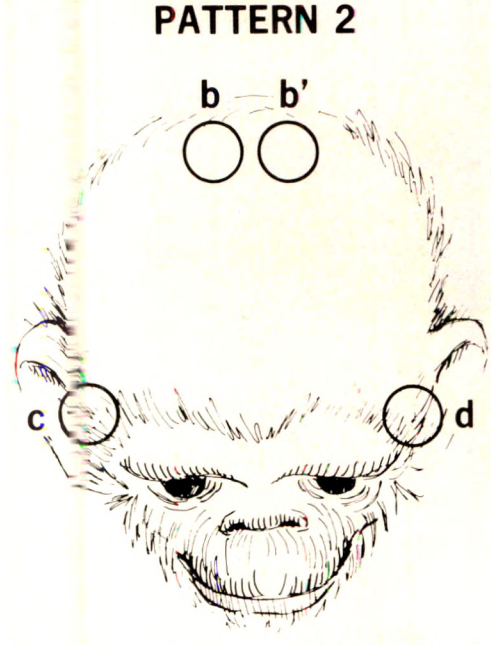


FIG 2. Pattern II. Using agar sponges 2.5 cm in diameter on the skin surface: electrodes b and b′ straddle the greater occiptal nerves c-2-3; electrodes c and d overlie the greater auricular nerves on their respective sides, anterior to the ear and about 3 cm lateral to and behind the lateral canthus of the eye. Milliamperage figures are average current; 20% duty cycle produces a peak current 5 times higher than the average current value. In none of the studies were the streams of current crossed, as in the interference pattern.

in any single application. The frequency between any pair of electrodes was 50 to 100 pps (pulses/sec) different from the frequency between any other pair.

The test for anesthesia in this series was the response to the application of pain to the tail by an electric device which produces a low-frequency square pulse. When a strong stimulus, applied for 30 seconds, evoked no response such as body movement or tail twitching, an anesthetic state was assumed to be present. To avoid a "startle" effect which resembles moving in response to pain, current applied for pain production was applied cautiously, intensity being started at zero and increased slowly and steadily to a predetermined level, usually 50 ma. The electrodes for the pain stimulator were subcutaneous needles 7.6 cm apart, in the tail. This pain-producing device was developed on human subjects to "measure" anesthesia.* It does no injury to tissues, and the pain ends instantly when the current flow is stopped.

Monkeys were rested at least 2 hours between current application and were used no more than 2 days per week. With each current application, an evaluation was made of pupil size and response to a strong light.

RESULTS (tables 1 and 2)

In the Rhesus, EA can be produced by electrostimulation of the nerves about the ears and the greater occipitals; it is not necessary to stimulate the supraorbital nerves. When EA is produced by electrostimulation of the nerves in the posterior 2/3 of the scalp, meiosis does not develop during the current application, and pupillary light reflexes are normal.

Subcutaneous pairs of electrodes carrying 30 ma of current produced 3rd-degree burns between the electrodes in one animal. No burns were produced by surface electrodes. EA can be produced by passing current from the skin in front of the ear to the skin overlying the greater occipital nerves.

DISCUSSION

It is not necessary to pass current through the head to produce EA in Rhesus monkeys, nor is it necessary to subject the eyes and trigeminal branches to electrostimulation to produce EA in these animals.

In the Rhesus, in all applications of current where the current path is through the orbits, meiosis develops as the current intensity approaches that required to produce EA. In this study, when meiosis was not present, the pupillary light reflexes were intact, findings interpreted as indicating that the eyes are not being stimulated by current. This absence of change was noted when anteriormost preauricular electrodes were more than 2 cm behind the lateral canthus of the eyes.

In all these studies, the current was applied across the nerve path; studies in other species are needed to learn whether this is the most efficient application pattern. These pathway studies and those of the effects of distances between electrodes are difficult in the Rhesus because the head surface is so small, making surface electrodes, which must be 2.5 cm in diameter, to avoid current-density burns, difficult to position effectively.

Pattern II (fig 2) was developed because pattern I (fig 1), based on subcutaneous electrodes, could not be duplicated with sponges on the surface, and we wanted to test high frequencies which require higher amplitudes than subcutaneous needle electrodes will carry without burning.

The subcutaneous electrodes did not produce burns at low frequencies which required low intensities. In the 10 kHz range, the amplitude required for EA production was so high that the small amount of tissue (1 x 2 cm) could not dissipate the heat produced, and burns developed in 1 monkey. When we found the burns, we duplicated the electrodes and current application on the arms of 2 investigators. A burning sensation developed in 8.5 minutes (1 subject) and in 10 minutes (the other subject). This finding suggests that the lack of reaction from the monkey was because it was under anesthesia when the burn developed.

In the pattern of current application reported here, EA "fades," as it does when the current is applied through the head. The fading is managed, as reported earlier,[6] by reducing the frequency and amplitude. Relatively comfortable high frequencies, with the higher required amplitude, will produce EA. When an anesthetic state is produced, the frequency can be turned down into more efficient ranges (500 to 1000 Hz), and the amplitude can be reduced as well. Note that in monkey 601 (table 2) 10 kHz required 50 ma but 200 Hz required only 5 ma.

*Smith RH, Andrew JN: Gradable pain production. Proc Neuroelectric Conference, Las Vegas, March 1970.

TABLE 1

Results of Passing Current Between Subcutaneous Electrodes

Monkey number	Current passed between electrodes		Interelectrode distance	Frequency (Hz) and duty cycle or duration	MA	Meiosis graded 1-4	Light reflex	Anesthesia
43	a-a′ or b-b′ or c-c′	Horiz	2 cm	2000	12			No
	d-d′	pins		20%	15			
43	a-a′ + b-b′ + c-c′	Vert	5 cm	2000	10			Yes
	d-d′	pins		20%				
	anterior, close to eye							
43	a-a′ + b-b′		5 cm	2000	15			No
				20%				
43	c-c′ + d-d′		5 cm	2000	15			No
				20%				
601	a-a′ + b-b′ + c-c′		4 cm	1000-1500	6	1		Yes
	d-d′		d-d′ = 3 cm	20%	8	3-4		
601	b-b′ + c-c′ + d-d′		same	1000-1200	6	1	+	Yes
				20%	8	3-4	+	
600	b-b′ + c-c′ + d-d′		4 cm	1000 1100 1200	6	3 4	−	Yes
				20%				
600	c-c′ + d-d′		4 cm	1000-1100	6	4	−	Yes
				20%				
448	c-c′ + d-d′		3 cm	500-550				
	anterior 2 cm lateral to eye			20%				
600	b-b′ + c-c′ + d-d′		3 cm	1000-1100-1200	6	0	+	Yes
				20%				
600	same		3 cm	10K 10.5K 11K	30	0	+	Yes
				20%				

TABLE 2

Results of Passing Current Between Surface Electrodes

Monkey number	Frequency (Hz) and duty cycle or duration	ma	Meiosis	Light reflex	Anesthesia
448	500-550 0.2 ms dur	5	0	+	Yes
6	1000-1100 20%	15	0	+	Yes
601	500-550 20%	10	0	+	Yes
43	1000-1100 20%	15	1	+	Yes
448	5000-5500 20%	30	0	+	Yes
448	5000-5500 40%	40	0	+	Yes
448	10K, 10.5K 20%	50	0	+	Yes
448	10K, 10.5K 40%	60	0	+	Yes
6	10K, 10.5K 20%	60	0	+	Yes
6	1000-1100 20%	18	0	+	Yes
43	10K, 10.5K	65	0	+	Yes
43	1000-1100 20%	20	0	+	Yes
601	200-220 20%	5	0	+	Yes
601	10K, 10.5K 20%	50	0	+	Yes

All in pattern II. Agar sponges situated to move current between c and b and d and b'. Intersponge distance over 3 cm.

We have not tested in Rhesus monkeys the efficiency of EA by the parallel tests: surgical procedure and pain-stimulator, as was done in acute experiments on dogs, in which it was learned that the stimulator was a reliable means of predicting whether the animal would tolerate abdominal surgery without moving.

The anesthesia produced in this study was in no way different from that produced by the passage of current through the head. The items compared were reaction to the stimulator, fading, respiration and pulse, and muscle tone.

In these current applications, as in all others, the induction period is 1 to 5 minutes. The rate of increase in the current depends on the animals' respiratory rate. The struggling Rhesus frequently strains (Valsalva maneuvers), with slowing of the heart. When this occurs, the current is reduced slightly and the animal is ventilated 2 or 3 times, via endotracheal tube, with room air and a hand ventilator; then current buildup proceeds. When unconsciousness develops, the pulse rate and respiratory activity remain within normal range. A low-grade metabolic acidosis is present for the first 20 minutes, but Po_2 and Pco_2 are within normal limits. Muscle tone is not impaired, and the animal appears to be in the plane 3 of stage I of anesthesia.

We have learned, in the course of human experiments, that it is not possible to use 1 frequency output and divide it to energize 2 pairs of electrodes, even if the division is so adjusted as to be equal. Severe discomfort ensues: a form of vibration. Each pair of electrodes must have a frequency different from all other pairs, 50 to 100 pps being the usual difference. This finding necessitates 3 separate output channels for 3 pairs of electrodes.

The mechanism for the findings in this study is not clear. Earlier studies indicated that the "target area" probably was the thalamus,[3,9] or perhaps more properly, the thalamic area. We found some evidence that the EA state probably was consequent to depolarization. Our efforts for several years have been based on trying to get enough current into the critical area to produce the effect of continuous depolarization.

When current was being passed through the head in the usual manner of producing EA, an appropriate current density in some critical area was the objective. The discovery that a simple sensory nerve block prevented EA production changed the point of view on the necessity for an appropriate density. Now this discovery, that the passage of current across sensory nerves will produce EA, again raises the question of the necessity for a specific current density in the thalamic area.

Assume a monkey's head is 7.6 cm in diameter and 25 cm in circumference. If 3 electrode pairs are used, with 2 cm between each pair, there is some current getting into the brain center, but not much. If the interelectrode distance is 3 or 4 cm, a great deal more of the current is reaching the center of the brain. It is easy to assume that the portion reaching the brain center is responsible for the EA produced. However, if the sensory nerve is blocked with

a local anesthetic, the animal cannot be anesthetized with electric current. When surface electrodes were used, the distance between the electrodes was such that a great deal of current must have reached the brain center. Still, when the interelectrode area was infiltrated with local anesthetic, EA could not be produced.

It may be that the findings described here simply represent another means of providing the required stimulus in the appropriate area, in this case by overstimlation of the thalamus via high sensory-nerve input. Further neurophysiologic evaluation will be required for a more precise explanation.

Our laboratory has for over 9 years recommended that new electric current effects be evaluated by application to humans before application to animals. The pain-stimulator, the subcutaneous electrode introducer, and the crossover pattern of high frequencies were all developed in and on human subjects before being used on animals. Their acceptance in humans attests to their humane quality in lower animals.

ACKNOWLEDGMENT

The authors wish to thank the staff of the San Francisco General Hospital for their courtesy and cooperation.

REFERENCES

1. Kano T, Cowan GSM, Smith RH: The role of the somatosensory system in general electroanesthesia. Anesth & Analg 53:667-671, 1974

2. Zouhar RL, Tatsuno J, Smith RH, et al: Electroanesthesia studies: causes of fading of electrical anesthesia in the rhesus monkey. Anesth & Analg 46:307-310, 1967

3. Tatsuno J, Zouhar RL, Smith RH, et al: Electroanesthesia studies: the target area for electroanesthesia. Anesth & Analg 46:432-439, 1967

4. Andrew JH, Linquist PA, Smith RH: Electroanesthesia studies: cerebral blood flow and oxygen utilization during electroanesthesia in the rhesus. Anesth & Analg 52:464-469, 1973

5. Smith RH, Gramling ZW, Smith GW: Electronarcosis by a combination of direct and alternating currents. Effects on dog brain as shown by EEG and microscopic study. Anesthesiology 22:970-973, 1961

6. Smith RH, Andrew JH, Suzuki H, et al: Electroanesthesia studies: a new current pattern and control of fading. Anesth & Analg 47:627-632, 1968

7. Smith RH, Richard RK, Richter WR: Electrical anesthesia produced by combining direct and alternating currents: electron-microscopy of the dog brain. Anesthesiology 26:607-614, 1965

8. Richter WR, Zouhar RL, Tatsuno J, et al: Electron microscopy of the macaca mulatta brain after repeated applications of electric current. Anesthesiology 36:374-377, 1972

9. Tatsuno J, Zouhar RL, Smith RH, et al: Probe for determining current magnitude and pathway in the brain. Med Res Eng 7:38-41, 1968

Post-Thoracotomy Intercostal Block: Comparison of Its Effects on Pulmonary Function With Those of Intramuscular Meperidine

RONALD J. FAUST, MD
LEE A. NAUSS, MD
Department of Anesthesiology
Mayo Clinic and Mayo Foundation
Rochester, Minnesota 55901

Study of 34 patients who had undergone thoracotomy revealed that the group given intercostal nerve block analgesia had a significantly smaller decline in vital capacity after operation than did the group given narcotic analgesia only. The postoperative increase in arterial CO_2 tension of the nerve block group also was significantly smaller than that of the narcotic group. The study suggests that intercostal nerve block for post-thoracotomy analgesia offers some advantage in preserving effort-dependent pulmonary function when compared with postoperative narcotic analgesia.

ABBREVIATIONS

Pa_{O_2} = arterial partial pressure of O_2 (torr)

Pa_{CO_2} = arterial partial pressure of CO_2 (torr)

VC = vital capacity

MMFR = maximal mid-expiratory flow rate

MVV = maximal voluntary ventilation

$(A\text{-}a)D_{O_2}$ = alveolar-arterial difference of oxygen tensions

PA_{O_2} = alveolar partial pressure of O_2 (torr)

P_{IO_2} = inspired partial pressure of O_2 (torr)

PA_{CO_2} = alveolar partial pressure of CO_2 (torr)

R = respiratory quotient

F_{IO_2} = fraction of O_2 in inspired air

AFTER thoracotomy or surgery of the upper abdomen, pain produces a sequence of undesirable effects on respiratory function. Splinting and the inability to cough effectively cause retention of sputum and progressive atelectasis. These, in turn, may lead to ventilation-perfusion inequality, shunting, and hypoxemia.[1] More recent work implicates a decrease in functional residual capacity and airway closure in this process.[2]

Although narcotics make the pain more bearable and decrease the splinting of the chest wall, they depress the reflex urge to sigh. Even with narcotic doses that do not depress ventilation, the natural sigh mechanism is obtunded, thereby contributing to atelectasis.[3]

For more than 30 years, attempts have been made to overcome this postoperative pain problem by using regional analgesia.[4,5] Because afferent pain fibers can be blocked completely, local anesthetics may provide more nearly complete analgesia than systemically administered narcotics. If chest and abdominal wall movements are less painful after regional block, the postoperative patient might be able to breathe more deeply. Epidural and intercostal techniques have been used to achieve this analgesia, but studies comparing the pulmonary effects of narcotic analgesia with the pulmonary effects of regional techniques have shown conflicting results. In comparisons between groups receiving epidural analgesia and groups receiving narcotics, several investigators have found significant improvement in arterial oxygen tension but conflicting changes in dynamic lung volumes.[6-8] One recent study found similar decreases in Pa_{O_2}, Pa_{CO_2}, vital capacity, and peak expiratory flow rate when it compared groups given peridural analgesia with those given morphine after upper abdominal surgery.[9]

Regional analgesia has been studied less often after thoracotomy than after upper abdominal surgery. In 1966, Bergh and others[10] found significant improvement in peak expiratory flow rates in patients who were given an intercostal block the morning after thoracotomy. When compared with patients given narcotic analgesics only, the patients given intercostal block had significant changes in arterial oxygenation. More recently, Galway et al. found no improvement in lung volumes and no significant analgesic effect in patients given a transpleural intercostal block during thoracotomy.[11]

The purpose of our study was to compare pulmonary function in postoperative thoracotomy patients given either intercostal block or parenteral narcotics for analgesia.

METHODS

Thirty-four patients scheduled for thoracotomy were randomly allocated into two groups for postoperative analgesia: an intercostal nerve block group and a narcotic group.

Preoperative pulmonary disease and the specific surgical procedure planned were not determinants in group allocation, as long as a thoracotomy incision would be used. After obtaining informed consent, arterial blood gases were drawn the evening before surgery. Vital capacity, maximal mid-expiratory flow rate, and maximal voluntary ventilation were measured with a 9-liter Collins spirometer. All measurements were performed with the patient breathing room air and in a 45° semi-sitting position. No changes were made in the routine preoperative, surgical, or anesthetic management of the patient.

After surgery, each patient received routine nursing care until relief of pain was requested. The patient was then given either an intercostal nerve block or an intramuscular injection of a narcotic depending on the preoperative group assignment. Patients in the nerve block group had injections into seven intercostal spaces, according to the technique described by Moore.[12] A dose of 4 ml of bupivacaine (0.5%) with epinephrine (1:200,000) was placed into each of the five interspaces that were closest to the intercostal incision and into two interspaces at the level of the insertion of the chest tube. Patients in the narcotic group were given meperidine intramuscularly in a dose based on the surgeon's clinical estimate of the needs of the patient. The mean meperidine dosage was 0.92 mg/kg in these 17 patients (SE 0.09 mg/kg; range 0.61 to 1.47 mg/kg). Although it would be ideal to study the post-thoracotomy patient before and after he was given analgesia, the severity of the pain in these patients precluded accurate spirometry before analgesia. Thus, each patient was studied preoperatively and 45 minutes after the first administration of analgesia. Each measurement consisted of an arterial blood sample and spirometry. All measurements were performed with the patient breathing room air for at least 25 minutes and in a 45° semi-sitting position. All patients received chest physiotherapy and frequent cough encouragement throughout their postoperative course. Both groups of patients were followed to determine postoperative course, complications, and length of hospitalization.

Arterial gas results and results of spirometry were corrected for patient temperature. The alveolar-arterial difference of oxygen tension [$(A\text{-}a)D_{O_2}$] was calculated from the alveolar air equation: $P_{A_{O_2}} = P_{I_{O_2}} - P_{A_{CO_2}} \left(F_{I_{O_2}} + \frac{1 - F_{I_{O_2}}}{R} \right)$, in which R was assumed to be 0.8.

RESULTS

Thirty-four patients were studied; 17 were allocated to the intercostal nerve block group and 17 to the narcotic group. Patients requiring mechanical ventilation after operation were excluded. A higher incidence of females was noted in the narcotic group than in the nerve block group (8 of 17 patients compared with 3 of 17 patients). The average age of the patients in the intercostal block group was 63 years and of patients in the narcotic group, 61 years. When preoperative spirometry values were compared with the predicted normal value for each patient, the narcotic group had slightly higher mean vital capacity, maximal mid-expiratory flow rate, and maximal voluntary ventilation values than did the intercostal block group (Table 1), but the differences were not significant. Eighty-eight percent of the intercostal nerve block group and 65% of the narcotic group had resection of lung parenchyma during thoracotomy; in the remaining patients, the thoracotomy was performed for repair of a hiatal hernia or resection of an esophageal malignancy.

TABLE 1

Preoperative and Postoperative Spirometry* and Arterial Blood Gas Results for Intercostal Block Group and Narcotic Group (Mean ± SE)

	Intercostal block group (17 patients)			Narcotic group (17 patients)		
	Preoperative	Postoperative	Preop-Postop	Preoperative	Postoperative	Preop-Postop
VC	101.6 ± 5.2	41.8 ± 4.7	59.8 ± 4.8†‡	108.9 ± 3.7	31.1 ± 2.3‡	77.8 ± 4.8†
MMFR	61.9 ± 7.7	40.2 ± 6.2	21.7 ± 5.4†	69.7 ± 7.3	39.9 ± 4.5	29.8 ± 6.8†
MVV	83.9 ± 6.8	38.7 ± 4.5	45.2 ± 5.6†	94.4 ± 5.8	36.9 ± 4.0	57.5 ± 5.7†
Pao_2 (torr)	77.9 ± 3.2	65.4 ± 3.4	12.6 ± 2.8†	78.5 ± 3.4	68.4 ± 2.6	10.1 ± 4.0†
$Paco_2$ (torr)	34.9 ± 0.7	37.9 ± 1.1	−3.0 ± 1.0†‡	33.1 ± 0.9	38.6 ± 0.8	−5.5 ± 0.6†
(A-a)Do_2 (torr)	23.1 ± 3.0	32.2 ± 3.1	−9.1 ± 2.9†	24.7 ± 2.9	27.8 ± 3.1	−3.1 ± 3.8

*VC, MMFR, and MVV are expressed as % of predicted value; predicted values for each patient were derived from tables of normal spirometry data for our institution.

†Significant preop-postop difference within group ($p<0.05$).

‡Significant difference between groups ($p<0.05$).

Mean vital capacity, mean maximal mid-expiratory flow rate, and mean maximal voluntary ventilation were significantly decreased in both groups after operation ($p<0.05$, Student's *t*-test for paired data). Pao_2 decreased and $Paco_2$ increased in each group after operation, and these changes were also significant ($p<0.05$). In each of the three variables measured by spirometry after operation, the narcotic group had a greater decrease than did the intercostal block group, but the difference was statistically significant ($p<0.05$) only for vital capacity (fig 1). In spite of a slightly larger mean vital capacity before operation, the narcotic group had a mean decrease of 78% in vital capacity after operation. The mean decrease for the intercostal nerve block group was only 60%, however, and this was a significant difference between groups ($p<0.05$, Student's *t*-test).

The narcotic group showed slightly greatmean maximal voluntary ventilation before operation, but function decreased 58% after operation (fig 2). The intercostal nerve block group had a decrease of only 45% after operation, but the difference between groups was not statistically significant.

The narcotic group showed slightly greater maximal mid-expiratory flow rate before operation but a greater decline after operation—30% as compared with 22% for the intercostal nerve block group (fig 3).

Mean Pao_2 declined 13 torr in the intercostal block group and 10 torr in the narcotic group after operation (fig 4). $Paco_2$ increased 6 torr in the narcotic group and

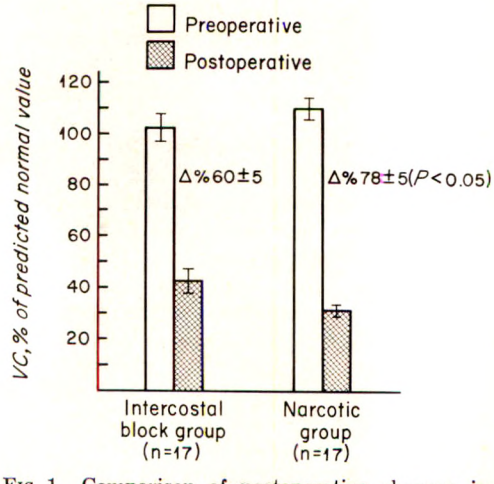


FIG 1. Comparison of postoperative changes in mean vital capacity (VC) between intercostal block group and narcotic group.

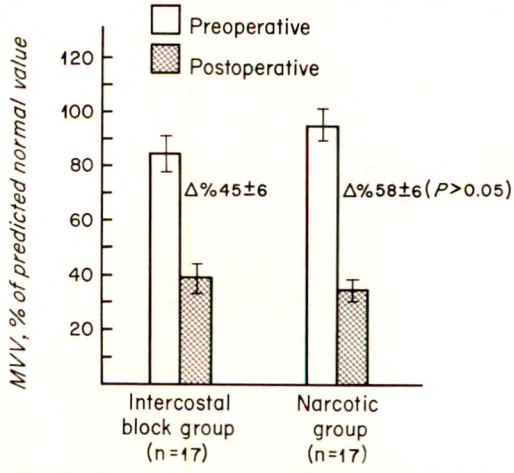


FIG 2. Comparison of postoperative changes in mean maximal voluntary ventilation (MVV) between intercostal block group and narcotic group.

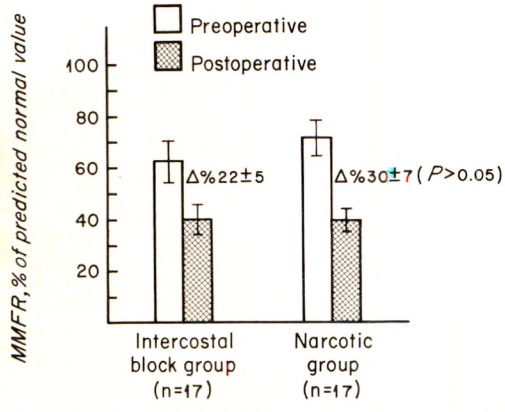


FIG 3. Comparison of postoperative changes in mean maximal mid-expiratory flow rate (MMFR) between intercostal block group and narcotic group.

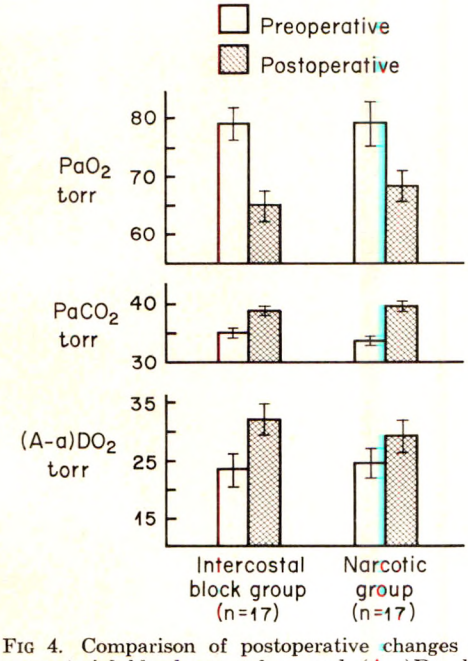


FIG 4. Comparison of postoperative changes in mean arterial blood gas values and (A-a)Do_2 between intercostal block group and narcotic group.

3 torr in the intercostal block group, and this difference between groups was statistically significant ($p<0.05$), although neither group showed postoperative CO_2 retention. The (A-a) Do_2 increased in each group after operation, but the difference was not significant between the groups.

Comparison of the length of hospitalization for the two groups showed no significant difference. There was one death in the nerve block group, death being due to nonpulmonary complications. Two patients in the narcotic group developed postoperative atelectasis that was evident roentgenographically. No complications were attributable to the intercostal nerve blocks themselves.

DISCUSSION

Our spirometry data reveal that one parameter of pulmonary function could be significantly improved after thoracotomy with intercostal nerve blocks. The significant improvement of vital capacity between the nerve block group and the narcotic group is perhaps explained on the basis of the vital capacity being an effort-dependent test of pulmonary function. The patients in the intercostal nerve block group may have been more capable of cooperating with our requests at the time of spirometry. The intercostal nerve block likewise probably improved the ability of these patients to cooperate with the cough and deep-breathing requests. Nevertheless, our data for maximal mid-expiratory flow rate and maximal voluntary ventilation did not show a statistically significant difference between groups. Our data agree with those of Bergh et al.,[10] who found a significant improvement in peak expiratory flow rates in patients who were given a single intercostal nerve block the morning after thoracotomy. Peak expiratory flow rate is another effort-dependent test of pulmonary function.

Our arterial blood gas data also agree with those from Bergh and associates' study, that is, no change in Pao_2 but a decrease in $Paco_2$ 2 hours after intercostal block the morning after thoracotomy. Our results differ from those of several investigators,[6-8] who found improved arterial oxygenation when regional analgesia was used after upper abdominal surgery.

Although we did not evaluate subjective pain relief, we have the clinical impression that intercostal block gave superior analgesia. Patients who have had both forms of analgesia frequently commented that the intercostal nerve block gave more effective pain relief. Although we considered an increase in vital capacity as an indication of improved pulmonary function, Bromage[5] interpreted increased vital capacity in itself as evidence of more effective analgesia. After the initial postoperative block, our patients were allowed to choose either a repeat block or a narcotic injection. Five of the 17 patients in the intercostal block group required no narcotics throughout their postoperative course, but these 5 requested repeat of their intercostal blocks an average of three times.

The patient who has had thoracotomy is an ideal candidate for intercostal block because the use of chest tubes decreases the danger of a pneumothorax, the most common complication of intercostal nerve block. This and the safety and long duration of action of bupivacaine itself have made intercostal nerve block a practical and safe approach to analgesia in the patient who has had thoracotomy.

Unlike that noted in a recent series from Seattle,[7] we found no significant difference in length of hospitalization between our two groups. A larger series might indicate whether hospitalization time or complication rate has been significantly altered by use of intercostal nerve block after thoracotomy.

ACKNOWLEDGMENTS

The authors would like to thank Dr. W. Spencer Payne and Dr. Philip E. Bernatz of the Department of Surgery of the Mayo Clinic for their cooperation in this study.

REFERENCES

1. Comroe J, Forster RE II, Dubois AB, et al: The Lung: Clinical Physiology and Pulmonary Function Tests. Second Edition. Chicago, Year Book Medical Publishers, 1962, pp 238-240

2. Alexander JI, Spence AA, Parikh RK, et al: The role of airway closure in postoperative hypoxaemia. Br J Anaesth 45:34-40, 1973

3. Egbert LD, Bendixen HH: Effect of morphine on breathing pattern: a possible factor in atelectasis. JAMA 188:485-488, 1964

4. Starr A, Gilman S: The effect of postoperative intercostal-nerve block on pulmonary ventilation. N Engl J Med 227:102-104, 1942

5. Bromage PR: Spirometry in assessment of analgesia after abdominal surgery: a method of comparing analgesic drugs. Br Med J 2:589-593, 1955

6. Muneyuki M, Ueda Y, Urabe N, et al: Postoperative pain relief and respiratory function in man: comparison between intermittent intravenous injections of meperidine and continuous lumbar epidural analgesia. Anesthesiology 29:304-313, 1968

7. Spence AA, Smith G: Postoperative analgesia and lung function: a comparison of morphine with extradural block. Br J Anaesth 43:144-148, 1971

8. Hollmén A, Saukkonen J: Zur postoperativen Schmerzausschaltung nach oberbauchoperationen. Narkotica, Intercostalblockade and Epiduralanaesthesie und deren Einfluss auf die atmung. Anaesthesist 18:298-303, 1969

9. Pflug AE, Murphy TM, Butler SH, et al: The effects of postoperative peridural analgesia on pulmonary therapy and pulmonary complications. Anesthesiology 41:8-17, 1974

10. Bergh NP, Dottori O, Löf BA, et al: Effect of intercostal block on lung function after thoracotomy. Acta Anaesthesiol Scand [Suppl] 24:85-95, 1966

11. Galway JE, Caves PK, Dundee JW: Effect of intercostal nerve blockade during operation on lung function and the relief of pain following thoracotomy. Br J Anaesth 47:730-735, 1975

12. Moore DC: Regional Block: A Handbook for Use in the Clinical Practice of Medicine and Surgery. Fourth Edition. Springfield, Illinois, Charles C Thomas, Publisher, 1965, pp 152-155

Changes in Blood Chemistries Following Prolonged Enflurane Anesthesia

E. I. EGER, II, MD*
R. K. CALVERLEY, MD†
N. T. SMITH, MD‡

Blood chemistries revealed minimal or no injury to the kidney or liver in 12 young healthy male volunteers subjected to 9.6 MAC hours of enflurane anesthesia without surgical stress. The results were similar to those previously obtained with halothane, isoflurane, fluroxene, and diethyl ether.

THE evaluation of the toxic effects of anesthetics in man usually is compromised by the (1) superimposition of surgical stress, (2) presence of preexisting hepatic or renal disease, and (3) clinical requirements for the use of adjuvant drugs. These additional factors can induce their own effects which may obscure the actions of the anesthetic. Studies in volunteers circumvent these limitations and therefore are of particular value since they allow the direct correlation of the changes seen with the anesthetic stress alone.

We recently obtained blood chemistries from 12 young (20 to 26 years) healthy male volunteers who underwent prolonged and occasionally deep (2 MAC) enflurane anesthesia in the course of cardiorespiratory studies. The following is a report of these studies and their results.

METHODS

Prior to anesthesia, blood specimens were drawn from the volunteers for the analyses listed in the table. Anesthesia was induced and maintained at 1.0, 1.5, and 2.0 MAC (infrared analysis) with enflurane in O_2 (9.6 ± 0.4 SEM MAC-hours§) with a brief addition of N_2O (an additional 0.6 MAC-hours) midway during the anesthesia. Except for the use of succinylcholine to facilitate endotracheal intubation, no other drugs were given. Anesthetic dose was reduced if systolic arterial pressure fell to 45 torr. Ventilation was controlled to maintain a normal $Paco_2$ for about 2/3 of the study and was spontaneous the remainder of the time. With spontaneous ventilation, $Paco_2$ sometimes reached 80 torr.

Blood specimens again were obtained the 1st and 5th days after anesthesia and were compared (paired *t*-test) with the preanesthetic results (table). We accepted as significant a p value of <0.05. Complete values were not obtained in all cases.

§MAC-hours were obtained by taking the sum of all doses times duration of exposure at each dose for a given subject and dividing by MAC[1] corrected for age[2] (.89% enflurane).

*Professor, Department of Anesthesia, University of California, San Francisco, California 94143.
†Assistant Professor, Department of Anesthesia, University of California, San Diego, California.
‡Professor, Department of Anesthesia, University of California, San Diego.

Read at the 50th Congress of the International Anesthesia Research Society, March 14-18, 1976, Phoenix, Arizona.
This work was supported by USPHS GM 15571 and a grant from Ohio Medical Products Division of Airco, Inc.
Paper received: 12/24/75
Accepted for publication: 2/18/76

TABLE
Effect of Enflurane on Blood Chemistries

Test (normal values)	N	Preanesthesia	Postanesthesia 1 day	Postanesthesia 5 days
BSP (less than 5%)	11	3.7 ± 0.4	4.1 ± 0.5	4.1 ± 0.5
SGOT (8-30 units/L)	11	22 ± 3	61 ± 18*	31 ± 8
SGPT (5-35 units/L)	11	19 ± 3	30 ± 7	28 ± 6
LDH (36-200 units/L)	10	125 ± 7	178 ± 18*	183 ± 21*
CPK (30-140 units/L)	4	75 ± 8	637 ± 250	156 ± 40
Bilirubin (less than 1 mg/dl)	11	0.6 ± 0.1	0.9 ± 0.2*	0.7 ± 1†
Alkaline phosphatase (4.5-11 units/dl)	10	6.5 ± 0.4	5.7 ± 0.2*	5.7 ± 0.4*
Creatinine (0.8-1.2 mg/dl)	12	1.0 ± 0.04	1.0 ± 0.03	1.0 ± 0.03
Blood urea nitrogen (8-23 mg/dl)	11	13.8 ± 0.8	9.5 ± 0.5*	15.2 ± 0.7*
Uric acid (3.4-6.4 mg/dl)	11	5.7 ± 0.2	6.2 ± 0.3*	6.6 ± 0.3*
Na^+ (135-145 mEq/dl)	12	140 ± 0.6	141 ± 0.4	140 ± 0.7
K^+ (3.5-4.5 mEq/dl)	12	3.8 ± 0.06	3.5 ± 0.05*	4.3 ± 0.09*
Cl^- (95-106 mEq/L)	12	105 ± 0.8	105 ± 0.6	101 ± 0.7*
Ca^{++} (9-10.6 mg/dl)	10	9.1 ± 0.9	8.7 ± 0.5	9.5 ± 0.2*
Total protein (6-8 g/dl)	11	6.8 ± 0.1	6.3 ± 0.2	7.7 ± 0.3*
Triglycerides	10	75 ± 12	83 ± 7	121 ± 19*
Cholesterol	11	170 ± 8	146 ± 6	174 ± 8

Values ± SEM.
*Significantly different from preanesthesia ($p<0.05$).
†N = 8.

RESULTS AND DISCUSSION

Although enflurane undergoes slight biodegradation to products which include fluoride ion,[3] there was little change in creatinine, blood urea nitrogen, or serum electrolytes, all of which remained within normal limits. The statistically significant (but clinically insignificant) rise in uric acid was nearly identical to that seen after prolonged halothane anesthesia in a similar group of volunteers.[4] Although the lower serum K^+ at 2 days was within normal limits, this decrease was not seen in previous studies following prolonged isoflurane or halothane anesthesia.[4]

Liver function studies gave somewhat conflicting results. Like isoflurane, enflurane did not significantly affect BSP retention at 1 day following anesthesia (table). This contrasts with the effects of halothane, fluroxene, and diethyl ether, which under similar circumstances of anesthetic duration and dose produced average values of 10, 8, and 10% retention, respectively (fig 1).[4] However, neither halothane nor isoflurane consistently increased SGOT or LDH in previous studies, whereas we found that enflurane did and, in the case of SGOT, enflurane gave an average value well above the normal range (table, fig 2).

Finally, in the 4 volunteers in whom it was measured, CPK rose consistently. The small sample size and variability of the increase precluded determination of statistical significance, but the results suggest the need for further study of this enzyme change.

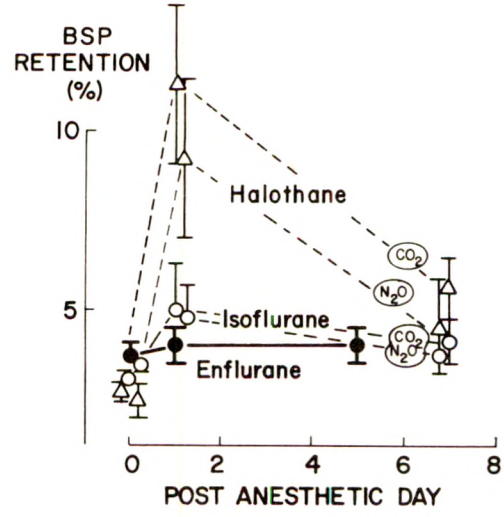


FIG 1. Data for enflurane for BSP retention (dark lines, filled circles) from this study are contrasted with data from previous studies[4] for halothane (dashed lines, open triangles) and isoflurane (dashed lines, open circles). Two groups of subject results are shown for both halothane and isoflurane. As indicated on the graphs, N_2O was added to the anesthetic regime in 1 case and CO_2 (to determine responsiveness to CO_2) in the other. All values are means ± SEM.

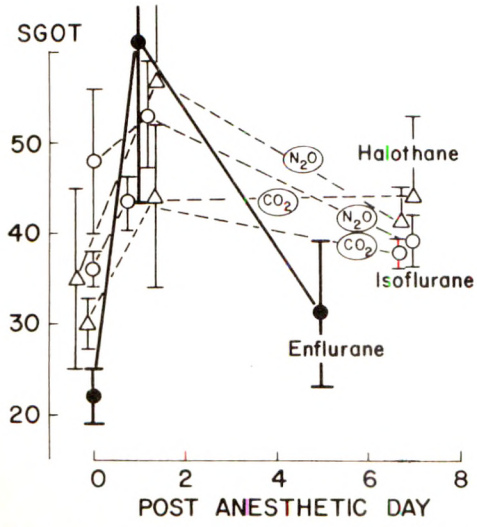


FIG 2. Comparisons from figure 1 are repeated here for SGOT. In contrast to the absence of an effect on BSP retention, enflurane (solid line) caused a significant rise in SGOT on the 1st post-anesthetic day. The increases in SGOT seen with halothane or isoflurane were not statistically significant.

CPK values are not available from previous similar studies. However, we recently have found* that halothane anesthesia in volunteers also is followed by an increase in CPK.

We conclude that prolonged and sometimes profound enflurane anesthesia in young healthy volunteers produces minimal changes in blood chemistries that reflect renal and hepatic function.

REFERENCES

1. Gion H, Saidman LJ: The minimum alveolar concentration of enflurane in man. Anesthesiology 35:361-364, 1971

2. Gregory GA, Eger EI II, Munson ES: The relationship between age and halothane requirement in man. Anesthesiology 30:488-491, 1969

3. Chase RE, Holaday DA, Fiserova-Bergerova V, et al: The biotransformation of Ethrane in man. Anesthesiology 35:263-267, 1971

4. Stevens WC, Eger EI II, Joas TA, et al: Comparative toxicity of isoflurane, halothane, fluroxene, and diethyl ether in human volunteers. Can Anaesth Soc J 24:357-368, 1973

Guest Discussion

WENDELL C. STEVENS, MD
Department of Anesthesia
University of California
San Francisco, California

Efforts by clinical studies to distinguish among the potent inhaled agents with respect to their toxicity to liver and kidney have not proven too fruitful. Perhaps this is good. For, put another way, all are quite safe. Anesthetic-induced depression and accompanying hypotension, even when severe as it was with all of the agents tested, did not result in injury sufficient to alter hepatic or renal function persistently. The rise of SGOT with enflurane, which had returned to control levels by the 5th post-operative day, might not be indicative of hepatic injury, since this enzyme is found in many tissues other than liver. Perhaps the absence of abnormality in somewhat more specific tests such as the BSP, SGPT, and LDH support this idea.

Studies such as these are important even though the results are not very exciting. For one thing, the anesthetic exposure was unusual in that no surgical stress occurred, yet prolonged anesthesia and the stress of elevated P_{CO_2} were imposed. Certainly the anesthetic exposure was as great as the vast majority of patients will encounter. Therefore, one can have reasonable confidence that injury from enflurane will not follow a simple dose-response relationship as a classic hepatotoxin or nephrotoxin should—confidence at least within the limits of the doses Dr. Eger administered.

Another feature of such broad testing is that a significant event may occur which warrants further tests. Since we are puzzled so frequently about the pathogenesis of anesthetic toxicity, no reasonable lead should be overlooked. In the current study, an elevation of CPK occurred. As Dr. Eger indicated, comparative data are not available to determine if this finding is unique to enflurane.

This study is encouraging specifically because no renal abnormality occurred. Both the type and quantity of metabolite produced by anesthetic metabolism are important in anesthetic toxicity. Enflurane metabolism yields inorganic fluoride. These long MAC-hour exposures did not produce sufficient free fluoride to result in hypernatremia or azotemia.

These studies can give us no confidence that enflurane will not produce a rare, serious hepatic injury such as occurs with halothane, but I am sure the authors would not expect such certainty from these studies. We will have to wait for information on which patients are at risk and/or what the anesthetic metabolites are which produce halothane's hepatotoxicity. Then we can predict what may happen with a new compound.

*Calverley RK, Smith NT: Unpublished data.

Spinal Anesthesia for Lumbar Disc Surgery: Review of 576 Operations

DAVID J. SILVER, MD*
REMBRANDT H. DUNSMORE, MD†
CHARLES M. DICKSON, MD‡
Hartford, Connecticut§

Neurologic complications accompanying spinal anesthesia were examined in 576 lumbar disc operations on 507 patients. The single serious complication did not seem attributable to the choice of anesthetic method. Minor neurologic complications, with the exception of spinal headache, could be explained by surgical manipulation. The authors conclude that spinal anesthesia is safe for surgical operations on the laterally herniated lumbar disc.

NEUROLOGIC complications associated with spinal anesthesia are rare and generally minor.[1-4] Controversy exists, however, over the use of spinal anesthesia for lumbar disc surgery. Vandam and Dripps[2] suggest that spinal anesthesia may exacerbate existing neurologic disease and recommend against its use for lumbar disc surgery. Others have found spinal anesthesia safe and effective.[5-8] Spinal anesthesia has been used at Hartford Hospital for more than 9000 disc operations during a 35-year period. We report here the results of a study of a sample of this patient population.

MATERIALS AND METHODS

From 918 lumbar disc operations at Hartford Hospital during 1969-70, the charts of 575 patients were selected randomly for study; 68 were eliminated because follow-up study was less than 6 weeks. Of the 611 procedures studied (399 on men and 212 on women), 576 were performed under spinal and 35 under general anesthesia. Patient ages ranged from 15 to 80 (average 43) years. One third were followed for more than 2 years and 55% for over 6 months. A myelogram preceded 77% of the operations. Average hospital stay was 7 days.

General anesthesia was employed in the following situations: (1) a near complete or total myelographic block; (2) inability to accomplish a subarachnoid tap; (3) myelographic demonstration of arachnoiditis; (4) inadvertent production of a "high spinal;" and (5) patient refusal of spinal anesthesia.

Approximately 93% of the operations under spinal were at the lowest 2 interspaces (table 1); only 81% of those done under general anesthesia were at the same spaces (table 2). In 58 operations, 2 herniated discs were removed. Each operated

*Chief Resident in Neurosurgery, Hartford Hospital; Instructor in Neurosurgery, Yale University.

†Associate Clinical Professor, Department of Surgery, University of Connecticut Health Center School of Medicine; Assistant Clinical Professor, Department of Surgery, Yale University School of Medicine; Chief, Department of Neurosurgery, Hartford Hospital.

‡Attending Anesthesiologist, Hartford Hospital.

§Departments of Neurosurgery and Anesthesia, Hartford Hospital, Hartford, Connecticut.
Reprint requests to Dr. Silver, 2800 North Vancouver Avenue, Suite 101, Portland, Oregon 97227.

Paper received: 9/23/75
Accepted for publication: 11/13/75

TABLE 1
Levels of Herniation of Patients Having Spinal Anesthesia

Level of herniation	Number	Percentage
L1-L2	2	0.3
L2-L3	9	1.4
L3-L4	32	5.1
L4-L5	328	51.9
L5-S1	261	41.3
Total	632	100.0

TABLE 2
Levels of Herniation of Patients Having General Anesthesia

Level of herniation	Number	Percentage
L1-L2	1	2.7
L2-L3	1	2.7
L3-L4	5	13.5
L4-L5	21	56.8
L5-S1	9	24.3
Total	37	100.0

TABLE 3
Summary of Recurrent Disc Operations Under Spinal

	Number of recurrences (104)			
	1	2	3	4
Number of patients (83)	67	12	3	1

level was counted separately.

More than 17% of the operations under spinal anesthesia were for recurrent disc herniation (table 3); 12 patients underwent 3 operations under spinal, 3 underwent 4, and 1 underwent 5.

Neurologic complications were carefully evaluated in an effort to separate surgical trauma from anesthetic damage. Motor or sensory deficit at a level different from that operated on, contralateral pain, or contralateral deficit was classified as a residual probably attributable to anesthesia.

TECHNIC OF ANESTHESIA

Anesthetic trays containing glass syringes, spinal needles, and small disposable needles which had been cleaned ultrasonically were wrapped and autoclaved in a central location. Single-dose vials of procaine, tetracaine, and ephedrine were packaged on the tray in a separate envelope marked on the outside with a sterilization indicator.

After the anesthesiologist inserted an IV catheter and checked vital signs, the patient was turned to the lateral position with the affected side down. The anesthesiologist scrubbed briefly, gloved, and painted the back with povidone-iodine solution. After local infiltration with procaine, a 22 or 25 spinal needle was introduced into the subarachnoid space in the midline at a level above the affected disc. A mixture of 10% procaine and 1% tetracaine (usually 8 to 10 mg tetracaine and 40 to 50 mg procaine), diluted to 2.5 to 3 ml with clear cerebrospinal fluid (CSF) was injected over 8 to 10 seconds. After injection, 0.1 to 0.2 ml of CSF was aspirated and reinjected to assure needle position. The patient was placed supine for 5 to 10 minutes, and the progression of anesthetic level carefully monitored. The operation was performed in the lateral position with the affected side up, after further skin infiltration with 1% lidocaine with epinephrine.

RESULTS

Under spinal anesthesia, 91.6% of patients achieved good-to-excellent results (table 4). All but 1 of the 8.4% fair and unsatisfactory results were so classified because of residual back pain. One patient, whose preoperative myelogram showed a large defect at L4-L5, had a moderate postoperative paresis of ankle flexors and extensors after unilateral exploration at the appropriate level. Reexploration 5 days later under general anesthesia revealed a large centrally herniated lumbosacral disc. The patient recovered to a "fair" status.

TABLE 4
Results of Surgery Under Spinal Anesthesia

	Number	Percentage
Excellent*	309	53.6
Good†	219	38.0
Fair‡	39	6.8
Unsatisfactory§	9	1.6
Total	576	100.0

*Totally asymptomatic.

†Mild back pain, unlimited activity.

‡Some limitation of activity, or change of job required.

§Persistent pain, severely limited activity, worsening of symptoms.

TABLE 5
Results of Surgery Under General Anesthesia

	Number	Percentage
Excellent*	17	48.6
Good†	7	20.0
Fair‡	4	11.4
Unsatisfactory§	7	20.0
Total	35	100.0

*Totally asymptomatic.

†Mild back pain, unlimited activity.

‡Some limitation of activity, or change of job required.

§Persistent pain, severely limited activity, worsening of symptoms.

Patients operated on under general anesthesia achieved 68.6% good-to-excellent results (table 5).

Of 11 patients graded fair or unsatisfactory, 7 had persistent pain and 4 had severe neurologic deficit. Two patients made unsatisfactory recoveries from preoperative paraparesis resulting from central disc herniation. Another sustained a bilateral footdrop after operation and the fourth, a unilaterial footdrop which partially recovered. The patients operated on under spinal anesthesia cannot be compared with those done under general anesthesia since those undergoing general anesthesia were clearly neurologically worse preoperatively.

Early complications following operations under spinal anesthesia (table 6) included 11 cases of increased neurologic deficit. Of the 5 patients with motor and sensory deficits, 3 had footdrop following L-5 root retraction, 1 had temporary saddle anesthesia after removal of a large central disc, and 1 suffered weakness of plantar flexion with associated calf dysesthesias after disc removal at the lumbosacral level. In the group with sensory changes only, 3 complained of persistent dysesthesias in a distribution consistent with the dermatome of the manipulated root and there were 2 cases of numbness of the contralateral thigh, probably from compression of the lateral femoral cutaneous nerve in the lateral operative position. A case of early contralateral postoperative pain was reoperated 2 months later with removal of an extruded fragment on the opposite side at the same level.

Other complications were infrequent (table 3). Only 1% of the spinals resulted in spinal headache. There were no wound infections. One CSF fistula, following a dural tear, was repaired at reexploration by reclosure of the lumbodorsal fascia. Trochanteric bursitis, found in 1%, likely resulted from pressure on the bursa in the lateral position.

TABLE 6
Early Postoperative Complications

Complications	Spinal (576 cases)	General (35 cases)
Increased neurologic deficit		
Motor and sensory change	5	3
Sensory change only	5	1
Contralateral pain	1	0
Urinary retention		
< 2 days	17	2
> 2 days	1	5
Pneumonitis or atelectasis	6	0
Phlebitis	4	0
Spinal headache	6	0
Aseptic meningitis	1	0
Discitis	1	0
Ileus	4	3
Wound problems		
Hematoma	2	0
Infection	0	0
CSF fistula	1	0
Trochanteric bursitis	5	0

The early neurologic complications associated with general anesthesia included 1 bilateral and 2 unilateral footdrops, and an instance of temporary dysesthesia in the distribution of a retracted S-1 root.

DISCUSSION

Operations on the herniated lumbar disc under spinal anesthesia produced results similar to those reported in other series. Several authors claim 90 to 95% good-to-excellent results in cases of typical radicular compression.[8-10]

Minor neurologic sequelae of spinal anesthesia have been estimated to occur in 0.5 to 0.8% of patients.[11,12] Since the majority of these relate to the lumbar and sacral dermatomes,[11] it is usually impossible to separate the complications produced by anesthesia from those related to surgical manipulation. Our 1 case of contralateral paresthesia was relieved upon removal of a contralateral recurrent disc.

The major reluctance to administer spinal anesthesia for lumbar disc surgery stems from fear of paralysis due to transverse myelitis or chronic progressive adhesive arachnoiditis. These entities are rare serious complications of spinal anesthesia,[12-14] occurring in less than 0.01% of cases. Progressive adhesive arachnoiditis may represent a nonspecific response to an intrathecal irritant.[11,13]

The patients surveyed in this study were, on average, older and had a higher percentage of herniated upper discs than has been found in a summary of 9082 cases from 30 reports in the literature.[7] Nearly 15% underwent 2 myelograms, and 17% had 2 or more disc operations under spinal anesthesia. Despite significant exposure to possible insult, chronic progressive adhesive arachnoiditis was not found. Indeed, 1 patient with known arachnoiditis had lysis of adhesions under spinal anesthesia, with clinical improvement. While this procedure is not recommended, our experience is in accord with that of Ditzler and associates,[5] who reported 10 patients with arachnoiditis to whom spinal anesthesia was administered without harmful effect. Our total experience of 9000 cases has led us to conclude that this feared complication of spinal anesthesia has not appeared more commonly in operations on the laterally herniated disc.

Five cases of significant neurologic residual were found in 3168 previously reported lumbar disc operations under spinal anesthesia (table 7). In Ditzler's series,[5] residual deficit related to application of concentrated nupercaine to the cauda equina. In Rosenberg's case,[6] progressive weakness developed in association with a deep wound infection and resolved with treatment of the infection. Spangfort's report[7] gave no information about the origin of the deficit.

Temporary urinary retention, as noted in table 3, was uncommon. Rosenberg and Berner[6] found urinary retention was more common after disc surgery under general anesthesia than under spinal. This observation has not been confirmed in a large randomly selected sample.

Our 1% incidence of postoperative headache was about 10% of that usually associated with spinal anesthesia. We hypothesize that epidural blood serves as a "patch," and reduces the dural leak.

One advantage of spinal anesthesia for the herniated disc may be decreased mortality. In the 4 series (table 7) employing spinal anesthesia for disc surgery, the 3 deaths represent a mortality rate of 0.08 percent. This is one-half that found in 15 recent reports of results of nearly 8300 cases of disc surgery.[7] In Hartford Hospital's 9000 cases of disc surgery under spinal anesthesia, there has been 1 postoperative death, from myocardial infarction, a mortality rate of 0.01 percent.

We conclude that proper administration of spinal anesthesia for the herniated lumbar disc is a safe procedure. Serious neurologic complications attributable to the anesthetic method have not been observed more frequently than when using spinal anesthesia for other operations. Low mortality and morbidity coupled with a short average hospital stay indicate to us that this is the anesthesia method of choice for such surgical operations.

ACKNOWLEDGMENT

The authors wish to thank Drs. James C. Collias, Norman H. Gahm, William B. Scoville and Benjamin B. Whitcomb for making available their records of the patients included in this study.

TABLE 7

Summary of Literature on Spinal Anesthesia for Lumbar Disc Surgery

	Operations	Significant neurologic residual	Mortality
Ditzler et al[5] (1959)	766	1	0
Rosenberg and Berner[6] (1965)	128	1	0
Spangfort[7] (1972)	2274	3	3
Subtotal	3168	5	3
Silver et al (1975)	576	1	0
Grand total	3744	6 (0.16%)	3 (0.08%)

REFERENCES

1. Dripps RD, Vandam LD: Long-term follow-up of patients who received 10,098 spinal anesthetics: failure to discover major neurological sequelae. JAMA 156:1486-1491, 1954

2. Vandam LD, Dripps RD: Exacerbation of pre-existing neurologic disease after spinal anesthesia. N Engl J Med 255:843-849, 1956

3. Sadove MS, Levin MJ: Neurological complications of spinal anesthesia: a statistical study of more than 10,000 cases. Ill Med J 105:169-174, 1954

4. Phillips OC, Ebner H, Nelson AT, et al: Neurological complications following spinal anesthesia with lidocaine: a prospective review of 10,440 cases. Anesthesiology 30:284-289, 1969

5. Ditzler JW, Dumke PR, Harrington JJ, et al: Should spinal anesthesia be used in surgery for herniated intervertebral disk? Anesth & Analg 38:118-124, 1959

6. Rosenberg MK, Berner G: Spinal anesthesia in lumbar disc surgery: review of 200 cases with a case history. Anesth & Analg 44:419-423, 1965

7. Spangfort EV: The lumbar disc herniation. A computer-aided analysis of 2504 operations. Acta Orthop Scand Suppl 142:1-95, 1972

8. Scoville WB, Corkill G: Lumbar disc surgery: technique of radical removal and early mobilization. J Neurosurg 39:265-269, 1973

9. O'Connell JEA: The indications for and results of the excision of lumbar intervertebral disc protrusions: review of 500 cases. Ann R Coll Surg Engl 6:403-412, 1950

10. Slepian A: Lumbar disc surgery: long follow-up results from three neurosurgeons. NY State J Med 66:1063-1068, 1966

11. Dripps RD, Eckenhoff JE, Vandam LD: Introduction to Anesthesia: The Principles of Safe Practice. Fourth edition. Philadelphia, WB Saunders Company, 1972, p 456

12. Thorsen G: Neurological complications after spinal anesthesia and results from 2493 follow-up cases. Acta Chir Scand Suppl 121:1-272, 1947

13. French JD: Clinical manifestations of lumbar spinal arachnoiditis: report of 13 cases. Surgery 20:718-729, 1946

14. Kennedy F, Effron AS, Perry G: The grave spinal cord paralysis caused by spinal anesthesia. Surg Gynecol Obstet 91:385-397, 1950

BICARBONATE DURING RESUSCITATION. Arterial pH, PCO_2 and osmolality were measured during cardiopulmonary resuscitation in dogs with or without intravenous sodium bicarbonate (1 mEq/kg). In the first 15 minutes of resuscitation pH did not fall below 7.35 and serum osmolality increased significantly when sodium bicarbonate was not administered to dogs. When bicarbonate was added to the regimen pH increased transiently, $PaCO_2$ increased and remained above awake levels and serum osmolality was elevated. These data confirm that adequate ventilation during resuscitation is sufficient to prevent the development of acidosis in the absence of pre-existing acidosis. $PaCO_2$ increased after bicarbonate despite adequate ventilation. These studies suggest that bicarbonate should not be used during cardiopulmonary resuscitation in the absence of (1) inadequate alveolar ventilation, (2) when cardiac arrest is brief and preexisting acidosis is unlikely or (3) in repeated doses without pH confirmation. Current recommendations of the National Conference on Cardiopulmonary Resuscitation are to administer bicarbonate 1 mEq/kg twice during the early minutes of resuscitation and repeat 0.5 mEq/kg at 10 minute intervals. *(Bishop RL, Weisfeldt ML: Sodium bicarbonate administration during cardiac arrest. Effect on arterial pH, PCO_2 and osmolality. JAMA 235:506-509, 1976)*

Hypoxemia and Hypocarbia Following Intermittent Positive-Pressure Breathing

FRED G. WRIGHT, JR., CAPTAIN, USAF (MC)*
MARY F. FOLEY, LT COL, (NC)†
JOHN B. DOWNS, MD‡
MICHAEL R. HODGES§

The authors determined the effects of short-term, vigorous intermittent positive-pressure breathing (IPPB) on arterial blood O_2 tension (Pa_{O_2}) in 10 unmedicated preoperative adult patients (ASA class I). Arterial blood was analyzed before and 0.5, 5, 15, and 40 minutes after 12 minutes of IPPB with nebulized 0.9% NaCl and room air. Pa_{O_2} increased from 89.1 ± 11 torr (mean ± SD) to 102.1 ± 13.9 torr, and arterial CO_2 tension decreased from 29.5 ± 4 torr to 18.4 ± 3 torr, causing significant respiratory alkalosis (pHa 7.62 ± 0.05). Five minutes after IPPB, Pa_{O_2} decreased to 69.2 ± 8 torr; alveolar-arterial P_{O_2} difference, breathing 21% O_2, increased significantly; and serum K^+ concentration decreased significantly. All these values returned to baseline levels within 40 minutes. The authors, acknowledging the value of IPPB when specifically indicated, counsel caution in patients with borderline pulmonary reserve and arterial oxygenation.

INTERMITTENT positive-pressure breathing (IPPB) is used widely as pulmonary therapy for postoperative patients and for patients with chronic lung diseases. Such therapy is thought to be beneficial, or at least to do no harm.[1] However, mechanically assisted, large tidal-volume breathing initiated in cooperative patients may cause alkalosis. Hypocarbia and alkalosis may decrease arterial blood O_2 tension (Pa_{O_2}).[2,3] Recently, hypoxemia has been described in patients with obstructive lung disease following IPPB.[4]

We initiated our study to determine the effects of short-term, vigorous IPPB in healthy preoperative adult patients with no evidence of preexisting pulmonary dysfunction.

METHODS

Ten unmedicated ASA class I patients, ranging in age from 20 to 35 (mean 28) years, were placed in semi-Fowler's position. A radial artery cannula was inserted percutaneously to facilitate blood sampling. Each patient received IPPB with room air for 12 minutes from a volume-preset ventilator (bird Mark 9-6) with an inspiratory pressure plateau of 0.8 seconds and a tidal volume of 12 ml/kg. Normal saline solution (5 ml) was added to the nebulizer. Patients

*Senior Resident, Department of Anesthesiology, Wilford Hall Medical Center, Lackland AFB, San Antonio, Texas 78236.

†U.S. Air Force Reserves.

‡Assistant Professor of Anesthesiology and Surgery, University of Florida College of Medicine and the Veterans Administration Hospital, Gainesville, Florida.

§Research Technician, Department of Anesthesiology, University of Utah College of Medicine, Salt Lake, City, Utah.

The voluntary, fully informed consent of the subjects used in this research was obtained, as required by AFR 169-8.

Paper received: 5/5/75

Accepted for publication: 11/26/75

were instructed to inhale, pause, then exhale at a comfortable respiratory rate (usually 14 to 18 breaths per minute). Pao_2, arterial CO_2 tension ($Paco_2$), and arterial pH (pHa) were measured with standard electrode technics* before and 0.5, 5, 15, and 40 minutes after IPPB. Alveolar-to-arterial O_2 tension difference breathing 21% O_2 ($A\text{-}aDo_2^{0.21}$) was calculated from the equation:[5]

$$A\text{-}aDo_2^{0.21} = FIO_2\ (PB - 47) - PACO_2\ (FIO_2 + \frac{1\text{-}FIO_2}{R}) - Pao_2$$

assuming a respiratory quotient (R) of 0.8 and alveolar CO_2 tension ($PACO_2$) = $Paco_2$. Barometric pressure (PB) was recorded prior to study and subjects received an inspired O_2 concentration (FIO_2) of 0.21 at all times. Serum K^+ concentrations were measured with a flame photometer,† hemoglobin by the cyanmethemoglobin method, and hematocrit by centrifugation at the times mentioned. At least 2 investigators were present during each study period. Data were analyzed by analysis of variance, a 2-tailed Student's *t*-test for paired data being used to determine significant differences from control values where indicated.

RESULTS

IPPB increased Pao_2 from 89.1 ± 11 (mean ± SD) torr to 102.1 ± 13.9 torr ($p<0.01$). $Paco_2$ decreased from 29.5 ± 4 torr to 18.4 ± 3 torr ($p<0.01$) and pHa increased from 7.44 ± 0.02 to 7.62 ± 0.05 ($p<0.01$) immediately after IPPB. Five minutes after discontinuing IPPB, Pao_2 values decreased to 69.2 ± 8 torr ($p<0.01$) and remained lower in every subject than pre-therapy values until the 40-minute sampling. $Paco_2$ and pHa were not statistically different from pre-IPPB values 5 minutes after therapy in any patient (fig 1, table).

$A\text{-}aDo_2$ was initially unchanged by IPPB, but increased significantly 5 minutes post-therapy from 19.5 ± 13.3 to 42.9 ± 7.3 ($p<0.01$) (table, fig 2). Serum K^+ was unaffected initially by IPPB and alkalosis, but fell from 3.6 ± 0.3 to 3.1 ± 0.3 mEq/L ($p<0.01$) 5 minutes after IPPB and gradually increased toward, but did not reach, pretherapy levels until the 40-minute sampling (table, fig 2). There were no significant changes in hematocrit, serum Na^+, or hemoglobin concentrations during the study.

Following IPPB, volunteers said that they felt slightly light-headed, but were otherwise comfortable. All patients appeared at all times to breathe without obvious hypoventilation or apnea.

DISCUSSION

Most patients were apprehensive before the study, which may explain why control pHa and $Paco_2$ values reflected respiratory alkalosis. Prior studies[6] have questioned the

*Instrumentation Laboratories model 113 analyzer.
†Instrumentation Laboratories model 143.

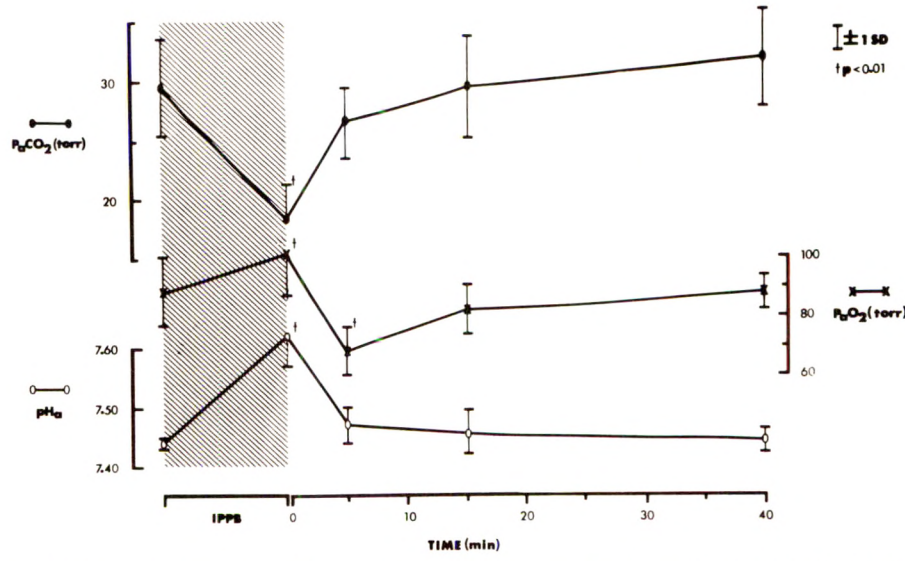


FIG 1. Arterial CO_2 tension ($Paco_2$), arterial O_2 tension (Pao_2), and arterial pH (pHa), before and after IPPB. Prestudy apprehension caused mild hyperventilation and respiratory alkalosis ($p<0.01$ compared with control values).

TABLE

Arterial O_2 Tension (Pao_2), CO_2 Tension ($Paco_2$), pHa, Serum Potassium Concentration (K^+), and Calculated Alveolar-Arterial O_2 Tension Difference (A-aDo_2) Before and 0.5, 5, 15, and 40 Minutes After 12 Minutes of IPPB (Mean ± SD)

	Control	Post-IPPB			
		0.5 min	5 min	15 min	40 min
Pao_2, torr	89.1 ±11.0	102.1* ±13.9	69.2* ±8.0	83.0 ±7.9	88.3 ±8.5
$Paco_2$, torr	29.5 ±4.0	18.4* ±3.0	26.7 ±3.0	29.6 ±4.6	31.5 ±4.0
pHa	7.44 ±0.02	7.62* ±0.05	7.47 ±0.03	7.45 ±0.04	7.44 ±0.02
K^+, mEq/L	3.6 ±0.3	3.6 ±0.3	3.1* ±0.3	3.4 ±0.2	3.5 ±0.2
A-aDo_2 $^{0.21}$, torr	19.5 ±13.3	21.5 ±13.6	42.9* ±7.3	26.8 ±9.1	17.8 ±8.1

*$p < 0.01$ when compared with control values.

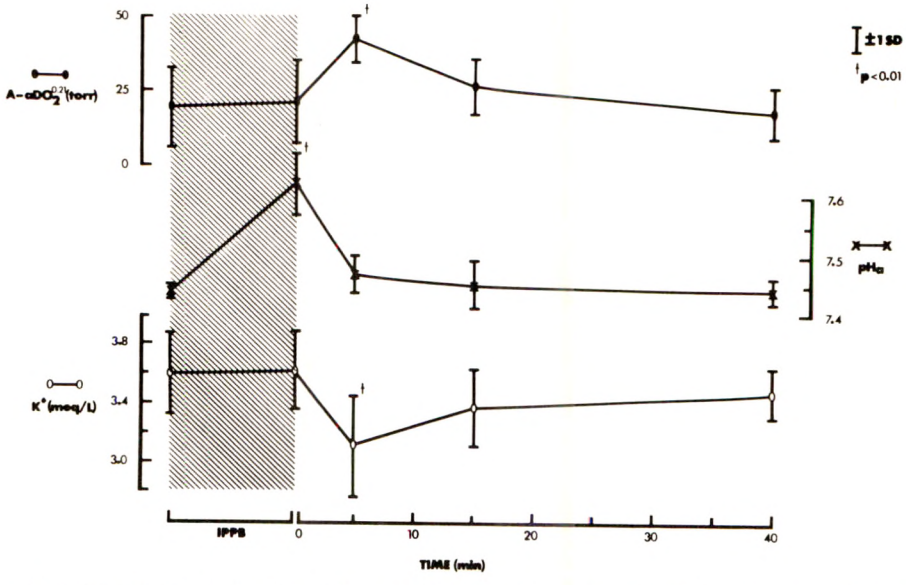


FIG 2. Alveolar-arterial O_2 tension difference (A-aDo_2 $^{0.21}$) during inhalation of room air, serum K^+, and pHa, before and after IPPB ($p<0.01$ compared with control values).

efficacy of postoperative IPPB therapy because of the inability of pressure-limited devices to deliver adequate tidal volumes. Therefore, we elected to use an IPPB volume approximately double the patient's normal spontaneous tidal volume. An inspiratory pressure plateau has been shown to produce increased alveolar distribution of inhaled gas,[7] and prior studies not using an inspiratory pressure plateau have been criticized.* Although we selected the tidal volume and inspiratory flow pattern, patients determined the respiratory rate and degree of hyperventilation. We assumed $PACO_2$ = $Paco_2$ and R = 0.8 in calculating A-aDo_2. If $PACO_2$ were actually less than $Paco_2$, changes in A-aDo_2 following IPPB would have been greater. Similarly, were R actually greater than 0.8, the post-IPPB increase in A-aDo_2 would have been greater. By these assumptions, we minimized calculated change in A-aDo_2 following IPPB.

There are numerous possible explanations for the observed fall in Pao_2 after IPPB.

*Bird F: Personal communication.

According to the Fick equation, [cardiac output = O_2 consumption ($\dot{V}O_2$)/arterio-mixed venous blood O_2 content difference ($Ca\text{-}\bar{v}O_2$)], $Ca\text{-}\bar{v}O_2$ is directly proportional to $\dot{V}O_2$ and inversely proportional to cardiac output. Pao_2 is inversely related to $Ca\text{-}\bar{v}O_2$ when Pao_2 is less than the PAO_2,[5] due to the transit of the mixed venous blood through a right-to-left shunt. Therefore, decreased cardiac output or increased $\dot{V}O_2$ may elevate $Ca\text{-}\bar{v}O_2$ and depress Pao_2.[8] Cherniack and associates[9] found that most cardiac output depression resulting from hyperventilation of anesthetized dogs occurred within the 1st minute. However, we observed no change in $A\text{-}aDo_2$ during hyperventilation (table, fig 2). If decreased cardiac output caused Pao_2 to fall in our patients, we would expect the effect to have occurred during hyperventilation, not 5 minutes later. An increase in $\dot{V}O_2$ also may have decreased Pao_2 without changing cardiac output.

Khambatta and Sullivan[10] found that respiratory alkalosis after 2 hours of hyperventilation caused $\dot{V}O_2$ to increase significantly but to return to normal within a 2-hour recovery period. Increased $\dot{V}O_2$ associated with alkalosis occurs both clinically[11] and experimentally.[12,13] It is unlikely that 12 minutes of hyperventilation was sufficient to increase O_2 consumption enough to account for the marked fall in Pao_2, but we cannot rule out the possibility. Both acute alkalosis and hypocarbia will cause a leftward shift in the oxyhemoglobin-dissociation curve and decreased Pao_2.[5] Since Pao_2 increased during the period of severe respiratory alkalosis and decreased during the recovery period, a shift in the oxyhemoglobin-dissociation curve probably played no significant role in changing Pao_2 in our patients.

Most investigators[2,3,9] have postulated that apnea or hypoventilation following prolonged hyperventilation is a potential source of hypoxemia. Our studies may show that hyperventilation partially depletes total body CO_2 content, but subsequent hypoventilation allows reaccumulation of these CO_2 stores. According to the alveolar-air equation, an increased $PACO_2$ will decrease PAO_2 and, therefore decrease Pao_2. In contrast, we found $Paco_2$ and, therefore, presumably $PACO_2$, less than baseline values when Pao_2 was lowest. Since $Paco_2$ did not increase in any patient after IPPB, calculated PAO_2 was not decreased and hypoventilation alone could not account for the decrease in Pao_2.

Mismatching of alveolar ventilation and perfusion ($\dot{V}A/Q$) may cause hypoxemia during inhalation of room air.[5] A decreased exchange of CO_2 in the presence of normal or slightly increased O_2 uptake at the alveolar level (marked decrease in respiratory quotient) may cause acute loss of alveolar volume and functional residual capacity (FRC) until normal CO_2-O_2 exchange is reestablished. Forrest[14] demonstrated in guinea pigs that the decrease in total alveolar volume following hyperventilation was related to the duration of hyperventilation but was maximal during the first 5 minutes. His findings complement those of McClenahan,[15] who reported that hyperventilation of adult rat lungs reduced the amount of effective pulmonary surfactant, thus promoting alveolar atelectasis, decreased FRC, and decreased lung compliance.

Nisbet and associates[16] compared the Pao_2 of 2 groups of dogs mechanically ventilated for 1 to 2 hours. One group was maintained at a normal $Paco_2$ and the other at a low $Paco_2$. The Pao_2 fell and the $A\text{-}aDo_2$ increased in the hypocarbic dogs, but these changes were not observed in the dogs with normal $Paco_2$. They attributed the difference in arterial oxygenation to decreased cardiac output, $\dot{V}A/Q$ inequality, or both. Hyperventilation-induced $\dot{V}A/Q$ mismatching probably explains the observed decrease in Pao_2 and increased $A\text{-}aDo_2$ in our patients.

Decreased serum K^+ during respiratory alkalosis has been reported previously.[17] Respiratory alkalosis will decrease cellular H^+ concentration, extracellular K^+ will enter cells to maintain cation balance, and serum K^+ will decrease. In our patients, the extravascular shift of K^+ lagged behind the pHa change, and serum K^+ remained below baseline values for up to 40 minutes, suggesting that a more complex relationship may exist between serum K^+ and pHa than previously reported. An acute fall in serum K^+ might have significant clinical implications in some patients with preexisting pathology (eg cardiac arrhythmias) or in those receiving medications such as diuretics and digitalis.

The purpose of this study was not to determine the efficacy of IPPB in patients with respiratory insufficiency. Our subjects were young, healthy, anxious, and unmedicated preoperative patients. Initial pHa and $Paco_2$ values indicated a state of acute hyperventilation, which may have exaggerated our findings. In this setting, IPPB resulted

in further hyperventilation, hypocarbia, and alkalosis, leading to significant arterial hypoxemia.

Patients with decreased pulmonary reserve and initially low Pao_2 may not respond in identical fashion. However, IPPB-induced acute alkalosis, hypoxemia, and hypokalemia in a previously compromised patient might be detrimental. For these reasons, we recommend IPPB be administered only when specific indications warrant its use. Furthermore, precautions should be taken to prevent hyperventilation, and to minimize the risk of hypoxemia, supplemental O_2 should be administered following therapy, especially in patients with borderline pulmonary reserve and arterial oxygenation.

ACKNOWLEDGMENT

We express our gratitude to the blood-gas technicians for aid in conducting the study, to Robert Fuchs for statistical assistance, Ms Cindy Bunt for secretarial assistance, Ms Dianna Kosman for editorial advice, and to J. H. Modell, MD, for his support.

REFERENCES

1. Petty TL: A critical look at IPPB. Chest 66:1-3, 1974

2. Sullivan SF, Patterson RW: Posthyperventilation hypoxia: theoretical considerations in man. Anesthesiology 29:981-986, 1968

3. Sullivan SF, Patterson RW, Papper EM: Posthyperventilation hypoxia. J Appl Physiol 22: 431-435, 1967

4. Lareau S: The effect of positive pressure breathing on the arterial oxygen tension in patients with chronic obstructive pulmonary disease receiving oxygen therapy. Am Rev Resp Dis 111:891-892, 1975

5. Comroe JH: Physiology of Respiration. Second edition. Chicago, Year Book Medical Publishers, 1974, chapters 2, 13, 14

6. McConnell DH, Maloney JV Jr, Buckberg GD: Postoperative intermittent positive-pressure breathing treatments: physiological considerations. J Thorac Cardiovasc Surg 68:944-952, 1974

7. Fulenihan S, Wilson R: Effect of mechanical ventilation with end-inspiratory pause on blood-gas exchange. Anesth & Analg 55:122-130, 1976

8. Bendixen HH, Egbert LD, Hedley-Whyte J, et al: Respiratory Care. St. Louis, CV Mosby Company, 1965, chapter 5

9. Cherniack NS, Longobardo GS, Staw I, et al: Dynamics of carbon dioxide stores changes following an alteration in ventilation. J Appl Physiol 21: 785-793, 1966

10. Khambatta HJ, Sullivan SF: Effects of respiratory alkalosis on oxygen consumption and oxygenation. Anesthesiology 38:53-58, 1973

11. Downs JB, Perkins HM, Modell JH: Intermittent mandatory ventilation. An evaluation. Arch Surg 109:519-523, 1974

12. Karetzky MS, Cain SM: Effect of carbon dioxide on oxygen uptake during hyperventilation in normal man. J Appl Physiol 28:8-12, 1970

13. Cain SM: Increased oxygen uptake with passive hyperventilation of dogs. J Appl Physiol 28:4-7, 1970

14. Forrest JB: The effect of hyperventilation on the size and shape of alveoli. Br J Anaesth 42:810-817, 1970

15. McClenahan J: Effect of respiration on surfactant, and its turnover rate. Clin Res 14:151, 1966

16. Nisbet HIA, Dobbinson TL, Steward DJ, et al: The effect of artificial ventilation on FRC and arterial oxygenation. 1. Rapid shallow ventilation at normal and low arterial carbon dioxide tensions. Can Anaesth Soc J 21:215-220, 1974

17. Flemma RJ, Young WG Jr: The metabolic effects of mechanical ventilation and respiratory alkalosis in postoperative patients. Surgery 56:36-43, 1964

Cardiovascular and Respiratory Effects of Isoproterenol Before and After Artificial Heart Implantation

WEN-SHIN LIU, MD*
THEODORE H. STANLEY, MD†
JESUS ISERN-AMARAL, MD‡
BRUCE WARD, PhD§
JUDD K. LUNN, MD‖
SCOTT GENTRY, BS**
STANLEY ATWOOD, BS††
Salt Lake City, Utah‡‡

Quantitation of peripheral vascular versus direct cardiac effects of isoproterenol (0.002 mg/kg) was attempted in a new pharmacologic animal model, the unanesthetized calf, before and after replacement of its natural heart with a pneumatically driven artificial heart (AH). Isoproterenol significantly increased ($p<0.01$) cardiac output and pulmonary shunt and decreased aortic blood pressure before and after AH replacement. Elevation of cardiac output and pulmonary shunt was greater ($p<0.05$) and depression of aortic pressure less ($p<0.05$) before AH replacement than after. Isoproterenol did not change pulmonary artery (PA) or right atrial (RA) blood pressures before AH implantation but did reduce ($p<0.05$) PA diastolic and mean pressures and increase mean RA pressures after. Systemic vascular resistance was significantly ($p<0.01$) reduced by isoproterenol before and after AH implantation. Heart rate, O_2 uptake, respiratory rate, tidal volume, and minute volume were all markedly increased before AH implantation but unchanged after. These findings demonstrate that approximately half the increase in output and pulmonary shunt and all changes in O_2 uptake and respiratory dynamics after administration of isoproterenol are related to cardiac effects of the drug. Our data also suggest that the unanesthetized bovine before and after AH replacement is a unique model for study of the differential pharmacology of drugs with respiratory, cardiac, and peripheral vascular effects.

RECENT advances in the development of an artificial heart (AH) to replace the natural heart of patients with uncorrectable or untreatable heart disease have made available a unique model for study of the differential cardiovascular and pulmonary effects of drugs with respiratory and cardiovascular actions.[1-4] This model, the unanesthetized calf before and after its natural heart is removed and replaced with a pneumatically powered, pulsatile artificial one, allows the direct cardiac effects of a drug to be differentiated from its actions on peripheral vasculature. Using the bovine AH model, we undertook the present study of the myocardial and peripheral vascular

*Fellow in Anesthesiology.
†Associate Professor of Anesthesiology.
‡Fellow in Anesthesiology.
§Assistant Professor, Biomedical Engineering.
‖Fellow in Anesthesiology.
**Research Assistant in Biomedical Engineering and Anesthesiology.
††Research Assistant in Biomedical Engineering and Anesthesiology.
‡‡Department of Anesthesiology, Institute of Biomedical Engineering and the Utah Biomedical Test Laboratory, University of Utah, Salt Lake City, Utah 84132.
Paper received: 8/8/75
Accepted for publication: 11/20/75

effects of a single IV 0.002 mg/kg dose of isoproterenol. In addition, the effects of isoproterenol on respiratory frequency, tidal volume, minute volume, O_2 uptake, and pulmonary shunt were also evaluated before and after AH implantation.

METHODS

The experimental subjects were 20 unanesthetized 80 to 104 kg bull calves. After induction of each animal with 3 to 5 mg/kg of IV sodium methohexital, intubation, and maintenance of anesthesia with 1 to 2% halothane, a 10-gauge needle was placed percutaneously into the right external jugular vein. With continuous pressure recording, a 7-Fr Swan-Ganz triple-lumen catheter was threaded through the needle, through the right ventricle, and into the proximal pulmonary artery. Another catheter (14 Fr) was placed percutaneously into the opposite external jugular vein and threaded into the right atrium. Following this, a small neck or groin incision was made and a third catheter (17 Fr) threaded into the central aorta through either the left carotid or left femoral arteries. Catheter position was documented by fluoroscopy and catheter patency maintained with a dilute heparinized (2 units/ml) solution of lactated Ringer's solution, administered at a rate of 1 to 2 ml/hr via a constant-infusion pump. Anesthesia was then terminated and the animals extubated and allowed to recover for 24 to 48 hours.

Pre-Artificial Heart Implantation Study Procedures.—Standing in a metal calf cage, the calf was allowed to breathe 100% O_2 through a specially designed airtight calf face mask. Inspiratory and expiratory J-valves (3 cm ID)* were attached to the mask portals and connected to an O_2 source. Pulmonary artery (PA) and aortic blood samples were obtained (for O_2 content analysis) after 20 minutes of O_2 breathing, and heart rate and systolic, diastolic, and mean PA and aortic and mean right atrial (RA) pressures were recorded. Oxygen uptake ($\dot{V}O_2$), respiratory rate (f), tidal volume (V_T) and minute volume ($\dot{V}$) were then measured over a 3-minute period by removing both J-valves from the mask portals; attaching one of the portals to a standard 9-liter, O_2-filled closed-circuit spirometer equipped with water and CO_2 absorbers; and plugging the other portal of the face mask.

*Warren E. Collins, model P-304.

$\dot{Q}_T$ was calculated using the Fick equation:

$$\dot{Q}_T = \frac{\dot{V}O_2}{Cao_2 - C\bar{v}o_2}$$

$\dot{Q}_S/\dot{Q}_T$ was determined from the modified shunt equation:

$$\dot{Q}_S/\dot{Q}_T = \frac{(PAo_2 - Pao_2) \times 0.0031}{(Cao_2 - C\bar{v}o_2) + (PAo_2 - Pao_2) \times 0.0031}$$

where $PAO_2 = PB - PH_2O - PaCO_2$

Blood Pco_2 was measured with a Severinghaus electrode, pH with a Radiometer glass electrode, and Po_2 with a modified Clark electrode. All electrodes were maintained at 39° C and frequently recalibrated with standard solutions and gases of known concentration and tension. Temperature corrections were made when necessary, using standard blood-gas correction factors. Oxygen saturation was determined on an AOC* oximeter and hgb on a Fisher hemophotometer. Rectal temperature was monitored with a Yellow Springs temperature probe and recording module. It was assumed that 1 gm of fully oxygenated calf blood combined with 1.39 ml of O_2.† Blood O_2 content in

*American Optical Company.

†It has been shown (Kosochi T and Stanley T, unpublished data) that freshly drawn, heparinized 12 to 16-week-old calves' blood will bind 1.38 to 1.41 ml of O_2/gm hgb when fully oxygenated.

ABBREVIATIONS AND SYMBOLS

AH = artificial heart
Cao_2 = O_2 content (ml) in 100 ml of arterial blood
$C\bar{v}o_2$ = O_2 content (ml) in 100 ml of mixed venous pulmonary artery blood
f = respiratory rate
Hgb = hemoglobin
LA = left atrial
PA = pulmonary artery
PAo_2 = partial pressure of O_2 in alveolar air
Pao_2 = partial pressure of O_2 in arterial blood
$PA\text{-}ao_2$ = alveolar-arterial O_2 tension difference
$PaCO_2$ = partial pressure of CO_2 in arterial blood
PB = barometric pressure
PH_2O = partial pressure of water in respiratory alveoli (47 torr)
PVR = pulmonary vascular resistance
$\dot{Q}_S/\dot{Q}_T$ = pulmonary shunt
$\dot{Q}_T$ = cardiac output
RA = right atrial
SVR = systemic vascular resistance
$\dot{V}$ = minute ventilatory volume
V_D/V_T = dead space/tidal volume
$\dot{V}O_2$ = O_2 uptake
V_T = tidal volume

volumes percent were calculated from the hgb capacity, O_2 saturation, and dissolved O_2, according to the equation:

O_2 content = (1.39 × gm hgb/100 ml blood) + 0.0031 × Pao_2.

SVR was calculated from the equation:

$$SVR = \frac{\text{mean aortic blood pressure} - \text{mean RA pressure}}{\dot{Q}_T}$$

Following control measurements and with the calves breathing into the spirometer, 0.002 mg/kg of isoproterenol was rapidly given IV and after 1 minute, PA and aortic blood samples recollected; $\dot{V}O_2$, f, V_T, $\dot{V}$, heart rate and PA, aortic and RA blood pressures remeasured; and $\dot{Q}_T$ and $\dot{Q}_S/\dot{Q}_T$ recalculated. Two days later, each calf had his natural heart replaced with a pneumatically driven artificial heart.

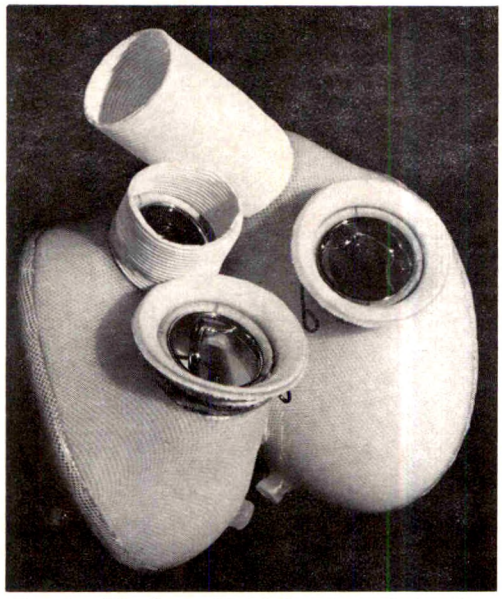


FIG 1. Silastic artificial heart used in these experiments.

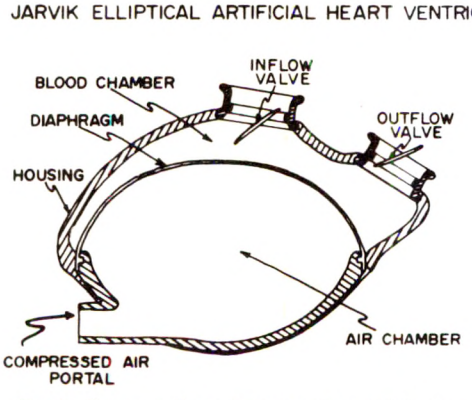


FIG 2. Cross-section of pneumatic artificial heart.

Design of Artificial Heart and AH Driving System.—A silicone rubber* or polyurethane elliptical type of AH (fig 1), previously described,[1-4] was used. Composed of 4 chambers (2 artificial atria and 2 artificial ventricles), it contains 4 Bjork-Shiley pyrolytic-carbon disc valves and weighs approximately 300 gm. Each ventricle (fig 2) consists of a rigid outer casing and a pliable inner blood-containing chamber, between which compressed air is applied for compression and ejection of blood.

An intrinsic AH control system (also previously described[1-4]) is based on the maintenance of relatively normal atrial pressures. This system basically consists of 2 direct-acting, 3-way solenoid valves in the control module, which apply compressed air through the 2 air-drive lines during systole and, during diastole, exhaust air to the atmosphere. With this system, the rate of filling and, therefore, the volume of blood entering each ventricle during diastole increases with an increase in atrial pressure. This volume is expelled during the next ventricular systole. As filling of the ventricle diminishes, so does stroke volume. There is, thus, an inherent balance between the pulmonic and systemic circulatory systems, as with the natural heart, and extremes of high and low atrial and venous pressures are avoided.

Artificial Heart Implantation Procedures.—All calves were anesthetized with 350 to 500 mg of sodium methohexital, intubated, and ventilated with O_2 at volumes of 1500 to 2000 ml/breath and rates of 10 to 14/min with a volume-limited respirator. Anesthesia was maintained with intermittent 2 mg/kg doses of ketamine and 0.5 mg/kg doses of succinylcholine IV. After a right lateral thoracotomy, removal of the Swan-Ganz and RA catheters, and placement of cardiopulmonary bypass catheters in the right carotid artery and inferior and superior jugular veins, cardiopulmonary bypass was initiated.

The natural heart was then excised, leaving the right lateral portion of the right atrium with both vena caval orifices and the bases of both atria. Silastic artificial left and right atria were sutured to the remnants of the natural atria. The artificial heart was then attached to the natural PA and aorta by standard woven Dacron arterial grafts and to the artificial atria by a quick-connect cinch mechanism. The PA

*Silastic®, silicone rubber of the Dow-Corning Company, Midland, Michigan.

and aortic grafts and artificial RA and left atrium (LA) contained Silastic taps, to which pieces of high-pressure IV tubing were connected and brought outside the chest for blood sampling and pressure monitoring.

Post-Artificial Heart Implantation Protocol and Study Procedures.—The calves were extubated 12 to 16 hours after AH implantation and all were eating, drinking, and behaving normally 24 to 36 hours later. They received no medications except gentamicin and/or penicillin thereafter. Post-implantation studies were initiated 4 to 36 days after AH implantation when V_T was >400 ml, $Paco_2$ <45 torr and Pao_2 >70 torr for 6 or more hours while breathing room air. Additional criteria for acceptance in the study included a $\dot{Q}_S/\dot{Q}_T$, and mean PA, aortic, and RA pressures within 20% of pre-AH levels when AH cardiac output was adjusted (via AH rate changes) to approximate preimplantation values.

When these requirements were met, each animal was allowed to breathe 100% O_2 through the calf face mask and the pre-AH implantation study procedures repeated. An additional parameter available for measurement post-AH implantation was mean LA pressure. The latter was obtained, as was RA, PA, and aortic pressures and blood samples, from high-pressure tubing connected to taps on the artificial atria and vascular grafts attaching the artificial ventricles to the natural PA and aorta. With mean LA pressure, it was possible to calculate pulmonary vascular resistance (PVR) after AH implantation, using the equation:

$$PVR = \frac{\text{mean PA pressure} - \text{mean LA pressure}}{\dot{Q}_T}$$

RESULTS

There was no significant difference in any parameter measured during control conditions (before administration of isoproterenol) prior to and after AH implantation (tables 1 and 2). Isoproterenol significantly ($p<0.01$) increased $\dot{Q}_T$ and $\dot{Q}_S/\dot{Q}_T$ and decreased systolic, diastolic, and mean aortic blood pressure before and after AH replacement. Elevation of $\dot{Q}$ and $\dot{Q}_S/\dot{Q}_T$ was markedly greater ($p<0.05$), and depression of aortic blood pressure significantly less ($p<0.05$), before AH replacement than after. Correlation of changes in $\dot{Q}_S/\dot{Q}_T$ with those in $\dot{Q}_T$ was good both before ($r=0.79$) and after ($r=0.84$) implantation. Isoproterenol did not significantly change systolic, diastolic, and mean PA or mean RA pressures before AH implantation. After implantation, systolic PA pressure was also unchanged by isoproterenol; however, diastolic and mean PA pressures were significantly ($p<0.05$) decreased and mean RA pressure significantly ($p<0.05$) increased.

SVR was reduced 48% by isoproterenol before AH implantation and 42% after. Both reductions were significant ($p<0.01$) but the difference between them was not ($p>0.2$). After AH implantation, PVR was reduced 31% by isoproterenol. PVR could not be calculated before implantation because LA pressure was not measured. Isoproterenol produced marked increases in heart rate (+119%), $\dot{V}O_2$ (+15%), f (+28%), V_T (+16%), and $\dot{V}$ (+48%) before AH implantation but made no significant change in any of these parameters after AH implantation. Arterial pH and $Paco_2$ were not significantly changed by isoproterenol either before or after AH implantation.

DISCUSSION

The mode of action and in particular the cardiovascular effects of the catecholamines have been extensively investigated for over 70 years.[5-7] These studies have demonstrated that isoproterenol, epinephrine, and norepinephrine have significant peripheral vascular effects, and that the first two also have profound direct positive inotropic and chronotropic actions on the myocardium. Additional studies[8-12] have shown that all 3 agents significantly increase respiratory rate, tidal volume, minute ventilation, and total body O_2 consumption; however, the influence of peripheral vascular versus direct cardiac effects of these drugs on cardiac output and respiratory dynamics has not been quantitated. The most important reason for this is that until now there has not been an intact experimental animal model that would permit such investigations. We believe that recent advances in the design and development of a pneumatically driven, pulsatile, artificial heart, which can be implanted into the chest cavity of 12 to 18-week-old calves, has made such studies feasible.

In this study, a single IV dose of 0.002 mg/kg of isoproterenol caused a 63% increase in $\dot{Q}_T$ before AH replacement and a 29% increase after. These findings indicate that 46%, or approximately half, of the increase in $\dot{Q}_T$ after this dose of isoproterenol in the calf with his natural heart intact is

TABLE 1

Effects of Isoproterenol on Cardiovascular Dynamics Before and After Artificial Heart Implantation in 20 Calves (Mean ± SD)

	Natural heart			Artificial heart		
	Before isoproterenol	After isoproterenol	Percent change	Before isoproterenol	After isoproterenol	Percent change
Cardiac output, L/min	9.3 ± 1.9	15.2* ± 2.2	+63 ±11	10.1 ± 2.4	13.0* ± 2.0	29‡ ±8
Heart rate	86 ± 8	192* ± 12	+119 ±12	90	90	0‡
Pulmonary artery						
Systolic BP, torr	31 ± 7	33 ± 6	+6 ±3	34 ± 10	33 ± 8	−3 ±2
Diastolic BP, torr	11 ± 4	11 ± 5	0 ±2	12 ± 3	8† ± 2	−33 ±9
Mean BP, torr	19 ± 4	20 ± 6	+5 ±3	21 ± 3	16† ± 3	−24 ±8
Aortic						
Systolic BP, torr	143 ± 12	128* ± 10	−10 ±4	147 ± 13	114* ± 11	−16‡ ±15
Diastolic BP, torr	92 ± 9	76* ± 9	−17 ±6	94 ± 9	70* ± 9	−25‡ ±9
Mean BP, torr	108 ± 10	93* ± 8	−14 ±5	111 ± 7	90* ± 8	−19‡ ±7
Left atrial pressure, torr				10 ± 2	7* ± 1	−30* ±9
Right atrial pressure, torr	6 ± 2	7 ± 2	+17 ±13	7 ± 2	10† ± 1	+42* ±12
Systemic vascular resistance (PRU)	11 ± 2	5.7* ± 1.3	−48 ±9	10.5 ± 1.8	6.1* ± 1.5	−42* ±11
Pulmonary vascular resistance (PRU)				1.0 ± 0.2	0.7* ± 1	−31* ±9

*$p<0.01$, Student's paired t-test when compared to pre-isoproterenol values.

†$p<0.05$, Student's paired t-test when compared to pre-isoproterenol values.

‡$p<0.05$, Student's paired t-test when compared to isoproterenol-induced changes before AH implantation.

TABLE 2

Effects of Isoproterenol on Respiratory Dynamics Before and After Artificial Heart Implantation in 20 Calves (Mean ± SD)

	Natural heart			Artificial heart		
	Before isoproterenol	After isoproterenol	Percent change	Before isoproterenol	After isoproterenol	Percent change
Pulmonary shunt, %	10.9 ± 3.1	16.1* ± 4.0	+48 ±10	12.1 ± 1.9	14.5† ± 2.4	+20‡ ±7
Minute volume, L/min	25 ± 6	37* ± 5	+48 ±14	26 ± 8	26 ± 7	0‡ ±6
Respiratory rate, breaths/min	32 ± 7	41* ± 8	+28 ±11	37 ± 10	38 ± 9	+2‡ ±7
Tidal volume, ml	781 ± 43	909* ± 51	+16 ±4	706 ± 50	695 ± 44	−2‡ ±6
O_2 uptake, ml/min	519 ± 37	595† ± 26	+15 ±5	515 ± 39	527 ± 44	+2‡ ±6

*$p<0.01$, Student's paired t-test when compared to pre-isoproterenol values.

†$p<0.05$, Student's paired t-test when compared to pre-isoproterenol values.

‡$p<0.05$, Student's paired t-test when compared to isoproterenol-induced changes before AH implantation.

achieved through peripheral vascular mechanisms, a decrease in arterial resistance and/or an increase in venous return. The profound arterial-dilating effects of isoproterenol secondary to beta-adrenergic stimulation are well known.[5-7] Less known, but possibly equally or more important, are the effects of this agent on capacitance vessels. Some have suggested that isoproterenol increases venous return by constricting capacitance vessels,[13] others that isoproterenol causes a dilation of such vessels.[14]

Green[15] has recently demonstrated that the immediate (within 1 min) effect of isoproterenol is to dilate the splanchnic outflow vessels, releasing trapped blood from the splanchnic bed. After 3 minutes, most of this increased blood volume is then redistributed via a reduction in peripheral arterial resistance from splanchnic to peripheral (muscular) compartments. Our protocol did not allow us to differentiate immediate (<1-min) changes in $\dot{Q}_T$ from those occurring at 3 minutes. Furthermore, the bovine AH animal model does not permit separation and quantitation, with any degree of accuracy, of changes in arterial resistance from changes in venous capacitance. However, it is clear from the large decrease in calculated SVR before and after AH implantation, and the significant increase in RA pressure after implantation but not before, that isoproterenol has a marked effect on both SVR and venous return.

Perhaps more important than differentiation between the direct cardiac effect of isoproterenol and its peripheral vascular effects is investigation of the influence of the drug on respiratory dynamics, particularly f, V_T, $\dot{V}$ and $\dot{V}O_2$. In this study, the latter were increased 28, 16, 48, and 15%, respectively, before AH implantation but not significantly changed after implantation. A number of other investigators[8-12,16-19] have had results similar to our pre-AH implantation findings in unanesthetized man and other animals. Cobbold and coworkers[8] found that 0.1 μg/kg of isoproterenol administered as a continuous infusion over a period of 30 minutes increased f a maximum of 30% and V_T 30 to 45% in man. Pulmonary $\dot{V}$ increased 66% within 5 minutes and subsequently fell to a level 30% above resting ventilation, a level maintained through the period of infusion. The changes in ventilation corresponded to increases in O_2 consumption and averaged 30% above control levels for the whole study. Similar, though less profound, respiratory changes have been found with infusions of epinephrine and norepinephrine.[9-12]

Although there have been many attempts to investigate catecholamine-induced hyperpnea, the mechanism is still unknown. Our findings in this study, while not demonstrating the exact cause of isoproterenol hyperpnea, do suggest that the mechanism is related to myocardial inotropic and/or chronotropic stimulation. Furthermore, they indicate that increases in $\dot{V}O_2$ after isoproterenol are not related to peripheral vascular effects of the drug or apparently to anything other than cardiorespiratory changes. Our data do not differentiate the percent of $\dot{V}O_2$ increase due to increased myocardial activity from that due to increased respiratory activity. However, it appears that $\dot{V}O_2$ changes after isoproterenol are not primarily due to $\dot{Q}_T$ alterations, since output increased an average of 29% after AH implantation but $\dot{V}O_2$ remained unchanged.

$\dot{Q}_S/\dot{Q}_T$ was markedly increased (+48%) before AH implantation and also significantly increased (+20%) after implantation. A number of investigators[16-19] have found significant increases in $\dot{Q}_S/\dot{Q}_T$ and $P_{A\text{-}a}O_2$ gradients after isoproterenol. Although the precise etiology remains uncertain, alveolar collapse and interference with hypoxic pressor responses have been attributed as mechanisms.[18] Palmer and Diament[20] have suggested that the primary cause of these changes is a decrease in airway resistance and an increase in physiologic dead space. It is difficult to conceive, in view of the significant difference in $\dot{Q}_S/\dot{Q}_T$ changes following isoproterenol before and after AH replacement, how the same dose of drug could cause less alveolar collapse, a greater hypoxic pulmonary pressor response, or a smaller decrease in airway resistance after AH implantation than before. It appears more reasonable, since correlation of changes in $\dot{Q}_S/\dot{Q}_T$ with those in $\dot{Q}_T$ were very high both before and after AH replacement, that $\dot{Q}_S/\dot{Q}_T$ changes after isoproterenol are more directly related to $\dot{Q}_T$ or pulmonary blood volume alterations and disturbances of ventilation and perfusion matching secondary to these changes.

Kreuzer[19] came to the same conclusion after showing that norepinephrine always produced significant decreases while epinephrine either decreased, increased, or yielded a biphasic $A\text{-}aDo_2$ response, depending on the dose of the amine used and presumably whether alpha or beta-adrenergic

stimulation predominated in his anesthetized dog preparations. He also suggested that a redistribution of blood from the pulmonary to the systemic circulations (as would probably occur after isoproterenol) or from the systemic to the pulmonary circulation (as would probably occur after norepinephrine) depended on the strength and duration of systemic and bronchial versus pulmonary vasoconstriction or vasodilation.

Absence of LA pressure measurements prevented calculation of PVR and comparison of changes in it with that of SVR during the pre-AH replacement periods of our study. However, comparison of these parameters post-AH replacement indicates that SVR was reduced to a greater degree than PVR, suggesting that pulmonary blood volume may have been decreased by isoproterenol after AH implantation despite an increased $\dot{Q}_T$. Whether pulmonary blood volume was also decreased by isoproterenol before AH replacement and, if so, whether it was decreased to a greater extent than after AH replacement, are questions that cannot be answered at this time. Likewise, it is impossible to determine from our data whether pulmonary blood volume changes (if they do indeed occur and are related to alterations in $\dot{Q}_S/\dot{Q}_T$) are important factors in the development of isoproterenol hyperpnea.

Perhaps, in spite of the absence of changes after AH implantation, alteration in $\dot{Q}_T$ is the principal determinant of isoproterenol hyperpnea. It is possible that significant changes in f, V_T and $\dot{V}$ occur only after a large change in $\dot{Q}_T$, and that 0.002 mg/kg of isoproterenol did not produce enough of an increase in AH output after AH implantation to alter any of these parameters. If this were the case, large changes in $\dot{Q}_T$, as produced by any mechanism, should induce hyperpnea.

Recent experiments in our laboratories have demonstrated that this is true.[4] Using the unanesthetized calf with an artificial heart and electively and nonpharmacologically changing heart rate (via a knob on the AH control module), we[4] found an ideal range of $\dot{Q}_T$ that minimized f, $\dot{V}$, $\dot{V}O_2$, $\dot{Q}_S/\dot{Q}_T$, and V_D/V_T and maximized V_T in each animal studied. The ideal range varied in width (from 1.2 to 2.6 L/min, or up to 37% of $\dot{Q}_T$) and in absolute numbers from animal to animal and in the same animal with change in position and metabolic state. Changes within the ideal range of $\dot{Q}_T$ did not produce significant changes in any of the above parameters. On the other hand, increases or decreases in $\dot{Q}_T$ out of the ideal range were almost always associated with increases in f, $\dot{V}$, $\dot{V}O_2$, $\dot{Q}_S/\dot{Q}_T$, V_D/V_T and decreases in V_T that were directly related to the magnitude of the $\dot{Q}_T$ alteration. It was suggested on the basis of these observations that there is an ideal range of $\dot{Q}_T$ which optimizes respiratory dynamics and minimizes $\dot{V}O_2$ for any given metabolic state.

These data and the results of this experiment raise a number of interesting questions. Can other noncatecholamines that produce profound effects in $\dot{Q}_T$ result in similar respiratory and $\dot{V}O_2$ changes? Is the hyperpnea of hypovolemic and cardiogenic shock related to $\dot{Q}_T$ changes? Does the hyperpnea of these entities differ from that resulting from isoproterenol? If $\dot{Q}_T$ alterations are the primary mechanism of catecholamine hyperpnea, is the pathway through the CNS or is it a direct effect on the lung?

These questions are unanswered at present but will have to be answered in the future if the mechanism of catecholamine-induced hyperpnea is to be finally understood. The AH-implanted bovine animal model may help in the solution of these problems, as well as in differentiation of the respiratory, cardiac, and peripheral vascular effects of any drug with cardiorespiratory actions.

REFERENCES

1. Kwan-Gett CS, Wu Y, Collan R, et al: Total replacement artificial heart and driving system with inherent regulation of cardiac output. Trans Am Soc Artif Intern Organs 15:245-250, 1969

2. Stanley TH, Volder J, Kolff WJ: Extrinsic artificial heart control via mixed venous blood gas tension analysis. Trans Am Soc Artif Intern Organs 19:258-261, 1973

3. Stanley TH, Oster H: The pulmonary effects of changes in left ventricular contractility. Surg Forum 25:191-192, 1974

4. Stanley TH, Liu WS, Amaral J, et al: Periodic pulmonary shunt analysis as a method of optimizing cardiac output after artificial heart implantation. Trans Am Soc Artif Intern Organs 21:353-360, 1975

5. Barger G, Dale HH: Chemical structure and sympathomimetic action of amines. J Physiol 41: 19-59, 1910

6. Knasnow N, Rolett EL, Yurchak PM, et al: Isoproterenol and cardiovascular performance. Am J Med 37:514-525, 1964

7. Aviado DM: Sympathomimetic Drugs. First edition. Springfield, Illinois, Charles C Thomas, Publisher, 1970, chapter 10

8. Cobbold AF, Ginsburg J, Paton A: Circulatory, respiratory and metabolic responses to isopropylnoradrenaline in man. J Physiol 151:539-550, 1960

9. Whelan RF, Young IM: The effect of adrenaline and noradrenaline infusions on respiration in man. Br J Pharmacol 8:98-102, 1953

10. Young IM: Some observations on the mechanism of adrenaline hyperpnoea. J Physiol 137: 374-395, 1957

11. Barcroft H, Basnayake V, Celander O, et al: The effect of carbon dioxide on the respiratory response to noradrenaline in man. J Physiol 137: 365-373, 1957

12. Coles DR, Duff F, Shepherd WHT, et al: The effect on respiration of infusions of adrenaline and noradrenaline into the carotid and vertebral arteries in man. Br J Pharmacol 11:346-350, 1956

13. Altura BM, Zwerfach BW: Evidence for beta receptors in the rat mesenteric microvasculature. J Pharmacol Exp Ther 150:23-25, 1965

14. Aviado DM, Wnuck AL, DeBeer EJ: Cardiovascular effects of sympathomimetic bronchodilators: epinephrine, ephedrine, pseudoephedrine, isoproterenol, methoxyphenamine and isoprophenamine. J Pharmacol Exp Ther 122:406-417, 1958

15. Green JF: Mechanism of action of isoproterenol upon venous return. Fed Proc 34:464, 1975

16. Fordham RMM, Resnekov L: Arterial hypoxaemia: a side effect of intravenous isoprenaline used after cardiac surgery. Thorax 23:19-23, 1968

17. Tai E, Read J: Response of blood gas tensions to aminophylline and isoprenaline in patients with asthma. Thorax 22:543-549, 1967

18. Muneyuki M, Urabe N, Kato H, et al: The effects of catecholamine on arterial oxygen tension and pulmonary shunting during the postoperative period in man. Anesthesiology 34:356-364, 1971

19. Kreuzer F: Influence of catecholamines on arterial oxygen tension in the anesthetized dog. J Appl Physiol 16:1043-1046, 1961

20. Palmer KNV, Diament ML: Effect of aerosol isoprenaline on blood gas tensions in severe bronchial asthma. Lancet 2:1232-1233, 1967

ASTHMA. An attempt was made to define criteria that would identify patients with acute asthma who should be managed as in-patients rather than outpatients. Asthma attacks not successfully treated in the emergency room were characterized by severe airway obstruction (peak flow rate less than 16% of the predicted) and a poor response to the initial epinephrine injection (0.3 ml subcutaneously) as evidenced by a peak flow rate improving less than 16% or remaining below 60 l/min. Accurate assessment of the degree of airway obstruction and subsequent responsiveness to bronchodilators (epinephrine and aminophylline) was not possible by clinical impression or physical examination. In the patients requiring hospitalization hypoxemia was modest and hypercarbia was not present. *(Banner AS, Shah RS, Addington WW: Rapid prediction of need for hospitalization in acute asthma. JAMA 235:1337-1338, 1976)*

The Local Anesthetic Activity of Tetrodotoxin Alone and in Combination With Vasoconstrictors and Local Anesthetics

H. JACK ADAMS, PhD*
MURRAY REID BLAIR, JR., PhD†
BERTIL H. TAKMAN, PhD‡
Framingham, Massachusetts§

Tetrodotoxin (TTX), alone and in combination with various vasoconstrictors and local anesthetics, was evaluated for its ability to produce peripheral nerve blocks in the rat and central neural blocks in the cat and dog. High frequency and long duration of block can be attained if sufficiently high concentrations of TTX are used, although latency is long and high dosage may produce systemic toxicity. Frequency and mean duration of block can be increased and systemic toxicity reduced if TTX is administered with a vasoconstrictive agent. Conventional local anesthetics also enhance the nerve-blocking activity of TTX. When appropriate concentrations of TTX and local anesthetics are used, a high frequency of blocks characterized by short latency and long duration can be demonstrated. The studies present some indirect evidence that local anesthetics enhance TTX activity by reversibly increasing the permeability of various neural barriers to TTX.

Most published studies on tetrodotoxin‖ (TTX) have been concerned with its site and mechanism of action, its effects on such structures as the neuromuscular junction, and its pharmacologic effects on isolated tissues and in whole animals.[1-4] Only a few have evaluated its remarkable local-anesthetic properties.[5-9]

Exploratory studies in our laboratory having indicated that conventional local anesthetics enhance the nerve-blocking activity of TTX, especially at those anatomic sites in which there are barriers to penetration, such as the dura mater and the neural sheath, we conducted studies to examine this phenomenon more fully.

METHODS

Isolated Frog Sciatic Nerve. — Sciatic nerve trunks of *Rana pipiens* were prepared (after the Camougis-Takman method[10]) by dissecting the nerve trunk from its roots in the spinal cord to the ankle and placing it on silver-silver chloride electrodes for stimulation of the nerve trunks and recording of the compound action potential at intervals throughout the blocking and recovery periods. Tasaki-Ringer solution (pH 7) was used both as a control medium and as a solvent for the test agents, and the nerve trunks were stimulated at 30 Hz. Based on exploratory studies, concentrations of lidocaine and of TTX were selected that produced a 5 to 15% block of the compound action potential after 30 minutes of exposure. Data were obtained on 7 nerve trunks exposed to 0.625 mM lidocaine, 8 exposed to 1 x 10^{-7} M of TTX, and 14 to a solution containing both lidocaine and TTX.

Rat Sciatic Nerve Blocks.—Precisely 0.2 ml of local anesthetic solution was injected

‖A toxin originally extracted, in 1950, from the ovaries of the globe fish (*Spheroides rubripes*) in Japan; LD_{50} in mice 10 μg/kg IP. *Ed.*

*Head, General Pharmacology Section.
†Director of Research.
‡Head, Chemistry Section.
§Research Department, Astra Pharmaceutical Products, Inc., Framingham, Massachusetts 01701.

Paper received: 6/9/75
Accepted for publication: 12/1/75

into the midthigh region of 1 hind limb around the sciatic nerve trunk. After injection, each animal was examined at intervals to ascertain frequency, onset, depth, and duration of block, as manifested by loss and recovery of motor function in the injected limb.

Frequency represents the number of successful blocks out of the total number of trials; *onset* is the time interval between the injection and the maximum degree of block obtained; and *duration* is the time interval between attainment of the maximum degree of block and either recovery of the ability to grasp or complete return of normal motor function. Frequencies, onsets, and durations given in the text and tables are for complete blocks resulting in total paralysis of the injected limb.

Five specific studies of rat nerve were conducted.*

1. TTX alone and with epinephrine.
2. TTX alone and with lidocaine.
3. TTX with lidocaine and with vasoconstrictors (phenylephrine, epinephrine, levonordefrin).
4. TTX and procaine.
5. TTX with local anesthetics.

Epidural Anesthesia in the Cat.—One male and 3 female cats, weighing 2.8 to 4 kg, were surgically prepared (by the method of Duce[11]) under anesthesia, by implantation of a polyvinyl catheter into a lumbar vertebra, for introduction of local-anesthetic solutions into the epidural space. Animals were allowed a minimum of 24 hours for recovery before tests. Each animal then received, on each of 3 consecutive days and in a randomized order, 1.5 ml of (1) 2% lidocaine; (2) TTX 1 μg/ml; or (3) 2% lidocaine with TTX, 1 μg/ml. All solutions contained 1:100,000 epinephrine.

Epidural Anesthesia in the Dog.—Adult male dogs, weighing an average of 10 kg, were surgically prepared (by the Lebeaux method[12]) under anesthesia, by implantation of a polyvinyl catheter into L-6 vertebra, for introduction of local-anesthetic solutions into the epidural space. All animals were allowed to recover for at least 24 hours before tests. Test solutions (5 ml) were administered at the rate of 1 ml/min, and animals were examined at frequent intervals for signs of onset of sensory analgesia and motor blockade. Examinations were continued at intervals until recovery from sensory and motor block was complete. The 2 hind limbs were evaluated independently for onset and duration of sensory analgesia and motor blockade. Each of 3 pairs of animals received 1 of the following 3 solutions: 2% lidocaine; TTX, 4 μg/ml; 2% lidocaine with TTX, 4 μg/ml. All solutions contained 1:100,000 epinephrine.

Solutions.—Stock solutions of TTX† (pH adjusted to 4-5) were prepared in distilled water and kept refrigerated. Dilute solutions for the studies were freshly prepared on the day of use, as were HCl solutions of the local anesthetics. Epinephrine, when employed, was added to the solutions immediately before use.

RESULTS

Isolated Frog Sciatic Nerve.—Lidocaine produced a mean block of 16% and TTX a mean block of 6%. The solution containing 0.625 mM lidocaine and 1×10^{-7} M of TTX produced a mean block of 47%, which is significantly greater ($p<0.01$) than that caused by either agent alone.

Rat Sciatic Nerve Blocks.

1. TTX Alone and With Epinephrine.—Epinephrine improved the frequency and increased duration of block at concentrations below 10 μg/ml. The toxicity of TTX was also reduced by the vasoconstrictor. No fatalities occurred at 10 μg/ml, and although all the animals given the 20 μg/ml solution died, the mean time to death in this group was 52 ± 12 minutes compared with 13 ± 2 minutes for the group given this concentration of TTX without epinephrine.

2. TTX Alone and With Lidocaine.—Neither TTX, 1 μg/ml, nor 0.1% lidocaine produced any blocks. However, a solution containing TTX and 0.1% lidocaine produced sciatic nerve block of 1 hour's duration in 66% of the animals. At 0.2%, lidocaine produced sciatic nerve block with a mean duration of 1 hour in only 50% of the animals, but a solution containing TTX and 0.2% lidocaine produced sciatic nerve block, with a mean duration of 79 minutes, in all the animals.

3. TTX With Lidocaine, Plain and With Vasoconstrictors.—The plain solution of TTX and lidocaine produced a block of

*Additional details available from senior author on request.

†Sankyo Company, Ltd.

about 3 hours duration in 1/5 of the animals injected. With the vasoconstrictors, frequency of block was 100% and mean duration about 6 hours. Unpaired *t*-tests showed that the onset time with levonordefrin was significantly longer than with phenylephrine ($0.02>p>0.01$) and epinephrine ($p<0.01$) but did not differ significantly between phenylephrine and epinephrine.

4. Temporal Relationship Between the Synergistic Effects of TTX and Procaine.—Procaine (2%) produced sciatic nerve block with a mean duration of 99 minutes. This duration was not affected by a subsequent injection of distilled water at 30 minutes. TTX, 1.5 μg/ml, produced no blocks in this experiment. The longest duration occurred when procaine and TTX were administered simultaneously. The mean duration of blocks became progressively shorter as the interval between the procaine and TTX injections was increased. TTX at 120 minutes had no effect; the mean duration of the procaine block was essentially the same as when procaine alone was given and when procaine was followed by distilled water.

5. TTX Administered Simultaneously With Various Local Anesthetics (table 1).—With TTX alone, frequency of block was only about 10% and the mean onset time was long. Frequency of block was 100% with all solutions containing both TTX and a local anesthetic, and mean onset times were virtually identical to those of the corresponding local anesthetics alone. However, mean durations of the solutions containing the 2 agents were 2½ to 5 times greater than with the corresponding local anesthetics.

6. Epidural Anesthesia in the Cat (table 2).—In general, frequency and duration of block were greater with the mixture of lidocaine and TTX than with either agent by itself.

TABLE 1
Rat Sciatic Nerve Blocks with TTX and Local Anesthetics

Agent	Concentration	Frequency of block	Onset* of block	Duration of block
Tetrodotoxin	2 μg/ml	2/20	13	151
Procaine	2%	5/5	2	60 ± 7
TTX:procaine	2 μg/ml:2%	5/5	2	314 ± 58
Lidocaine	2%	5/5	1	103 ± 37
TTX:lidocaine	2 μg/ml:2%	5/5	1	348 ± 17
Tetracaine	0.25%	4/5	6	62 ± 4
TTX:tetracaine	2 μg/ml:0.25%	5/5	5	296 ± 49
Dibucaine	0.125%	3/5	6	108 ± 25
TTX:dibucaine	2 μg/ml:0.125%	5/5	6	272 ± 56
Cocaine	0.25%	5/5	5	86 ± 17
TTX:cocaine	2 μg/ml:0.25%	5/5	5	361 ± 28
Bupivacaine	0.5%	5/5	4	133 ± 34
TTX:bupivacaine	2 μg/ml:0.5%	5/5	2	332 ± 52

*Mean onsets and durations are in minutes. SD is given for durations.

TABLE 2
Peridural Anesthesia in the Cat

Agent*	Concentration	Block of flexor reflex			Block of weight support		
		Frequency†	Onset‡	Duration§	Frequency†	Onset‡	Duration§
Lidocaine	2%	5/8	7	66 ± 19	8/8	2	88 ± 10
Tetrodotoxin	1 μg/ml	0/8	—	—	0/8	—	—
TTX:lidocaine	1μg/ml:2%	7/8	7	109 ± 8	8/8	<1	188 ± 9

*All solutions contained 1:100,000 epinephrine.
†Four animals, each hind limb evaluated separately.
‡Mean onset in minutes.
§Mean duration in minutes ± SD.

7. Epidural Anesthesia in the Dog (table 3).—Mean durations were essentially the same for TTX alone and TTX with lidocaine; they were, however, 2 to 2½ times longer than with lidocaine alone. Mean onset times for TTX were in general 2 to 4 times longer than with lidocaine. Of special interest is the observation that perception of noxious stimuli in the pudendal region, which was blocked in only one dog for about 2 hours with TTX, was blocked in both animals for a mean duration of about 5 hours with TTX and lidocaine.

DISCUSSION

TTX is an extremely potent agent capable, in microgram concentrations, of producing reversible blocks of long duration *in vitro* and *in situ*. Because of its low lipid solubility, it apparently penetrates with difficulty such barriers as the dura mater and the neural sheath around peripheral nerves. Evans,[9] for example, reported that TTX was ineffective when applied to peripheral nerves unless they were first desheathed, but that topical application of very low concentrations of TTX to the intradural portion of spinal roots produced conduction block, presumably because those roots lack a sheath. The studies reported here demonstrate that reversible nerve blocks of long duration can indeed be produced in peripheral nerves if sufficiently high concentrations of TTX are used.

As we observed in the rat sciatic nerve blocks, however, concentrations that produce a high frequency of successful blocks may also cause systemic toxicity and death. Vasoconstrictors in appropriate concentrations increase the frequency of successful blocks and reduce systemic toxicity and fatalities. The concomitant administration of classic local anesthetics also enhances the conduction blocking activity of TTX, as demonstrated in the studies of peripheral nerve blocks in rats and epidural anesthesia in cats and dogs. If suitable concentrations of TTX and local anesthetic agents are combined, these exhibit the short latency and high frequency of successful blocks characteristic of the local anesthetic and the remarkably long blocks characteristic of TTX.

It is possible to demonstrate what appears to be a true potentiation if the TTX or the local anesthetic, or both, are used at concentrations that are marginally effective or even ineffective. For example, neither TTX at 1 μg/ml nor 0.1% lidocaine effected any blocks when injected around the rat sciatic

TABLE 3

Epidural Anesthesia in the Dog

Agent	Concentration	Onset of block*				Duration of block			
		Flexor reflex	Sensory analgesia		Weight support	Flexor reflex	Sensory analgesia		Weight support
			Hind limbs	Pudendal area			Hind limbs	Pudendal area	
Lidocaine	2%	7 ± 0.5	7 ± 0.5	4.5	3 ± 2	115 ± 15	114 ± 15	118	148 ± 12
TTX	4 μg/ml	18 ± 6	14 ± 0.6	15†	12 ± 0	250 ± 96	224 ± 123	125†	406 ± 69
Lidocaine: TTX	2%: 4 μg/ml	8 ± 1	4 ± 2	4.5	3 ± 0	313 ± 84	316 ± 82	301	462 ± 72

*Onset and duration in minutes as means ± SD.

†Block in 1 of 2 animals only.

nerve trunk; when both were administered simultaneously, however, a better than 50% frequency of blocks was obtained with a mean duration of about an hour. It was also possible to demonstrate in the cat that a concentration of TTX that by itself produced no overt signs of epidural anesthesia doubled the duration of block produced by 2% lidocaine.

A further example can be singled out of the studies of epidural anesthesia in dogs. Analgesia in the pudendal area lasted for about 2 hours in the 2 animals tested with 2% lidocaine; TTX at 4 μg/ml effected block of this area for about 2 hours in only one dog. The solution containing both agents, however, produced sensory block in the pudendal area in both animals with a mean duration of 5 hours.

Lebeaux[12] has pointed out that, if the catheter is surgically implanted at L-6, the nerve roots mediating pain in this area are several spinal segments removed from the site of administration of the drug solution. The concentrations of TTX and lidocaine are, after diffusion from the site of administration and penetration through the barriers interposed between the epidural space and the spinal roots, lower than at the site of administration. Consequently, the synergistic effects of an adequate concentration of local anesthetic and a concentration of TTX that, on the basis of poor frequency, long onset, and relatively short duration, can be regarded as considerably less than maximally effective, are manifested as a block that is 2½ times longer than that produced by either agent alone.

The mode of action of the vasoconstrictors in enhancing the nerve-blocking effects of TTX seems clear. They decrease blood flow through the area, reduce systemic absorption, and thus maintain a higher concentration of TTX at the site of administration for a longer time. The mode of action of local anesthetics, on the other hand, is less obvious.

Staiman and colleagues[13] demonstrated a potentiation of TTX by lidocaine on frog nerve *in vitro*. In our studies with intact isolated frog sciatic nerve trunks we, too, have observed that blocks obtained with a mixture of lidocaine and TTX were significantly greater than with either agent alone and also greater than the sums of the blocks produced by these agents separately. Our studies also showed that local anesthetics enhanced the activity of TTX when injected around the sciatic nerve trunk in the rat and when administered epidurally in the cat and dog.

Therefore, the enhancement of the blocking activity of TTX in the presence of barriers such as the dura mater and the neural sheath suggests that, in addition to acting at different sites on the nerve membrane, as postulated by Staiman's group, TTX and lipid-soluble anesthetic agents may interact at another site: the neural barrier. The enhanced activity of the TTX may be due to an increase in permeability of the barrier to TTX brought about by the anesthetic agent. This would certainly explain the results obtained in our studies, but further studies are required to ascertain whether local anesthetics do indeed facilitate the movement of TTX across such barriers at the dura mater and the neural sheath.

The aim of the studies reported here was to examine the interaction of TTX and local anesthetics in various animal models and not to ascertain the potential clinical usefulness of these mixtures. However, the results do suggest the possibility that, with appropriate mixtures of TTX, a local anesthetic, and, for certain types of block, a vasoconstrictor, reversible blocks of long duration may be obtained with no more risk to the patient than with current blocking agents. Such a formulation would be highly desirable in those types of regional block in which prolonged relief of pain is the primary requisite.

ACKNOWLEDGMENT

The authors thank Mrs. Donna Charron and Miss Georgette Kilpatrick for their excellent technical assistance in conducting these studies.

REFERENCES

1. Halstead BW: Poisons and venomous marine animals of invertebrates. Washington, DC, US Government Printing Office, 1965, vol 1

2. Kao CY: Tetrodotoxin, saxitoxin and their significance in the study of excitation phenomena. Pharmacol Rev 18:997-1049, 1966

3. Evans MH: Tetrodotoxin, saxitoxin and related substances: their applications in neurobiology. Int Rev Neurobiol 15:83-166, 1972

4. Narahashi T: Chemicals as tools in the study of excitable membranes. Physiol Rev 54:814-889, 1974

5. Takahashi D, Inoko Y: Experimentelle Untersuchungen über das Fugugift. Arch Exp Pathol Pharmakol 26:401-418, 1890

6. Ishihara F: Über die physiologischen Wirkungen des Fugutoxin. Mitt Med Fak Tokio Univ 20:375-426, 1918

7. Iwakawa K, Kimura S: Experimentelle Untersuchungen über die Wirkung des Tetrodontoxins ("Fugugift"). Arch Exp Path Pharmakol 93:305-331, 1922

8. Ogura Y, Mori Y: Mechanism of local anesthetic action of crystalline tetrodotoxin and its derivatives. Eur J Pharacol 3:58-67, 1968

9. Evans MH: Topical application of saxitoxin and tetrodotoxin to peripheral nerves and spinal roots in the cat. Toxicon 5:289-298, 1968

10. Camougis G, Takman BH: Nerve and nerve-muscle preparations (as applied to local anesthetics), Methods in Pharmacology. Edited by A Schwartz. New York, Appleton-Century-Crofts, 1971, vol 1, pp 1-40

11. Duce BR, Zelechowski K, Camougis G, et al: Experimental epidural anaesthesia in the cat with lignocaine and amethocaine. Br J Anaesth 41:579-587, 1969

12. Lebeaux MI: Experimental epidural anaesthesia in the dog with lignocaine and bupivacaine. Br J Anaesth 45:549-555, 1973

13. Staiman A, Spero L, Seeman P: Different sites of membrane action for tetrodotoxin and lipid-soluble anesthetics. Proc Can Fed Biol Sci 17:160, 1974

DYSAUTONOMIA. Plasma norepinephrine concentrations and dopamine-beta-hydroxylase activity were measured in 10 normal patients and 10 patients with familial dysautonomia. After lying recumbent for 20 minutes plasma norepinephrine was similar in both groups. Normal subjects more than doubled their plasma norepinephrine after standing 5 minutes while dysautonomic patients did not increase their plasma norepinephrine. In dysautonomic patients blood pressure supine was similar to normals but fell nearly 50% with standing. Heart rate increased in controls but not dysautonomic patients during standing or isometric exercise. Blood pressure correlated with plasma catecholamine levels in dysautonomic but not normal patients. Dopamine-beta hydroxylase activity was reduced in dysautonomic patients. These data suggest that the spontaneous low activity of the sympathetic nerves is adequate to maintain normal plasma norepinephrine levels in dysautonomic patients. However, these patients do not release sufficient norepinephrine to provide circulatory adaptation to standing or exercise. *(Ziegler MG, Lake CR, Kopin IJ: Deficient sympathetic nervous response in familial dysautonomia. NEJM 294:630-633, 1976)*

A Dosage Nomogram for Sodium Nitroprusside-Induced Hypotension Under Anesthesia

NOEL W. LAWSON, MD*
DOLA S. THOMPSON, MD†
CARL L. NELSON, MD‡
JOAN W. FLACKE, MD§
ASTRIDE B. SEIFEN, MD‖
Little Rock, Arkansas**

Sodium nitroprusside (SNP) was used to produce deliberate hypotension in 30 selected patients, 9 to 78 years of age, for total hip replacement under halothane-N_2O-O_2 anesthesia. Hypotension was induced in the first 13 patients by infusing a 0.01% (100 μg/ml) solution of nitroprusside (NP) in 5% dextrose. Blood pressure was diminished to a level just producing a dry surgical field. Preliminary data demonstrated that the mean arterial blood pressure (MAP) achieving this condition was 65 torr ($p<0.01$) and that the minute dosage of NP (μg/min) required to consistently reduce MAP to 65 torr could not be predicted on the basis of body weight.

However, the age/weight ratio (yr/kg) of each patient, plotted against the known minute dosage of NP given during anesthesia, produced a highly significant dose-response curve ($p<0.001$, $r = -0.8226$).

The preliminary dose-response curve was examined in a double-blind study on an additional 17 patients. The curve derived from the prospective study did not differ from that of the preliminary study. In addition, the combined data from the retrospective and prospective studies (30 patients) gave a better statistical fit than did those from the preliminary study alone ($p<0.001$, $r = -0.8939$).

The nomogram provides an additional margin of safety in the use of this potent, fast-acting drug. SNP has been found predictable and effective in reducing surgical blood loss in selected patients undergoing total hip replacement.

SODIUM NITROPRUSSIDE (SNP) is a potent, rapid-acting, antihypertensive drug which produces arteriolar vasodilation by direct action independent of the autonomic nervous system.[1] Its short duration of action necessitates a continuous infusion to maintain a constant effect. These properties have made the drug useful in a variety of clinical situations.[2-4] In some centers, nitroprusside (NP) has been used to produce deliberate hypotension since 1962.[5] Other recent reports[6-9] indicate that this agent produces controlled hypotension which, in contrast to other methods, enhances tissue perfusion while effectively reducing surgical blood loss.

Our group has recently described a study[10] in which cardiac output and other circulatory parameters were measured in 13 patients undergoing total hip replacement, using halothane-N_2O-O_2 anesthesia and SNP-induced hypotension. Patient ages

*Associate Professor, Department of Anesthesiology.
†Professor, Department of Anesthesiology.
‡Professor, Department of Orthopedics.
§Assistant Professor, Department of Anesthesiology.
‖Assistant Professor, Department of Anesthesiology.
**University of Arkansas School of Medicine, Little Rock, Arkansas 72201.

Read at the 50th Congress of the International Anesthesia Research Society, March 14-18, 1976, Phoenix, Arizona.
Paper received: 3/22/76
Accepted for publication: 4/1/76

ranged from 9 to 78 years. Our results, confirming those of others,[6-9] indicated that NP produces a physiologically superior hypotensive state. Cardiac output rose toward normal during the hypotensive period. The increase was 20% above that of control patients undergoing the same procedure but kept normotensive. Urine output was not compromised and no arterial or venous acidosis was noted. Surgical blood loss was significantly reduced as a result of arterial hypotension, with a MAP of 64 ± 4 torr (± SE) resulting in a dry surgical field.

We noted, as have others,[7] that the NP dosage required to produce comparable levels of hypotension in a group of patients was not predictable on the basis of body weight. A better relationship existed between age and dose, although this correlation was not statistically significant either. However, analysis of the data revealed a highly significant correlation between a patient's age/weight ratio (yrs/kg) and NP minute dosage (μg/min) required to maintain levels of hypotension comparable to those attained in other patients. When the age/weight ratio for each patient in the earlier study was plotted against the minute dosage given, a highly significant ($p<0.001$, $r = -0.8226$) dose response resulted. This suggested that an appropriate dosage of NP could, in fact, be predicted (fig 1).

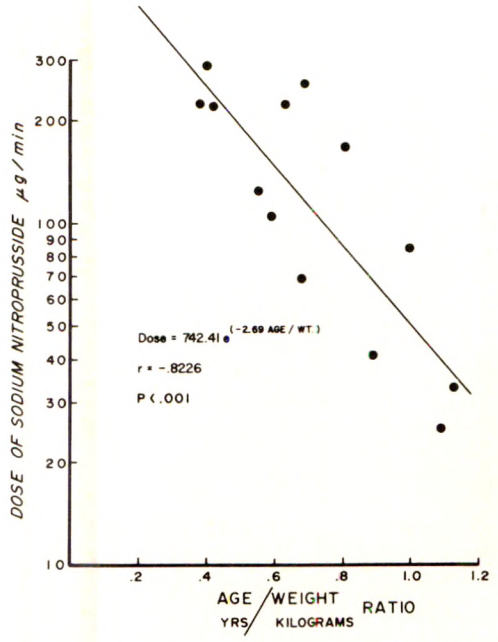


FIG 1. Highly significant dose-response curve resulting from retrospective analysis of age/weight ratios (yr/kg) plotted against the minute dosage of NP needed to maintain comparable levels of hypotension in earlier study.[10]

METHODS

Seventeen patients admitted for total hip replacement were studied. None of the subjects had evidence of cerebrovascular disease, clinical or electrocardiographic evidence of ischemic heart disease, anemia, renal hypertension, serious peripheral vascular disease, or severe obstructive lung disease. Advanced age was not considered a contraindication to deliberate hypotension during anesthesia.

Premedication consisted of appropriate doses of morphine, diazepam, and scopolamine, except in patients over 60, in whom morphine was omitted. Anesthesia was induced with 2% IV thiamylal and maintained with halothane (0.5 to 0.75%) in N_2O-O_2 (50:50). Patients were intubated after an appropriate dose of succinylcholine. A radial arterial cannula was inserted before the induction of anesthesia and the arterial blood pressure displayed continuously, along with the pulse rate and a lead II ECG, on a Tektronix® model 412 oscilloscope. In addition, the urine output, central venous pressure, and tympanic temperature were monitored. Arterial blood gases were sampled at 30-minute intervals throughout the procedure. A warming blanket was used to minimize heat loss.

Five percent dextrose in lactated Ringer's solution was given at a rate of 12 to 15 ml/kg during the 1st hour and at 6 to 10 ml/kg/hr thereafter. Homologous blood was administered only when a surgical blood loss of more than 500 ml was anticipated.

Continuous positive-pressure ventilation was not used as an aid in producing hypotension; instead, ventilation was assisted in order to maintain the $Paco_2$ between 37 and 41 torr. Nondepolarizing muscle relaxants were omitted, to avoid their possible hemodynamic effects. Patients remained supine during operation, with slight elevation of the hip. Blood loss was estimated from the content of the suction bottles and by weighing sponges. Irrigation fluid was collected in a separate suction system.

Three concentrations of SNP, 0.01% (100 μg/ml), 0.005% (50 μg/ml), or 0.0025% (25 μg/ml) in 5% dextrose, were used. One of these concentrations was assigned at random to consecutive patients, this variation being intended to prevent the study team from becoming familiar with the response

to only a single concentration. One anesthesiologist was assigned the responsibility for the induction and maintenance of hypotension in each case.

The person administering the NP had no knowledge of the concentration used or of the age/weight ratio of the patient. However, as a safety precaution, a starting volume (ml/min) was assigned. This volume was determined by the study leader, who knew the drug concentration being delivered, the age/weight ratio of the patient, and the NP dosage anticipated from the described dose-response curve. The study leader did not participate in the administration of the anesthetic or the NP after the initial order had been given.

Hypotension was induced just before skin incision. The NP solution was given through a peripheral IV catheter at an infusion rate controlled by an infusion pump,* allowing accurate control of the delivered volumes. Starting at the assigned volume, the rate of infusion was adjusted empirically to lower and maintain a mean arterial pressure (MAP) of ± 65 torr. This pressure was chosen, on the basis of our preliminary study, as being safe and effective in reducing surgical blood loss.

The infusion was discontinued and the blood pressure allowed to return to normal before wound closure in order to permit hemostasis. The duration of hypotension was measured from the time the desired level of pressure had been reached until the infusion was stopped. The total dose of NP administered over that time period was also recorded. The average minute dosage (μg/min) required to maintain each patient's MAP at 65 torr was calculated. This dosage was plotted on semilog paper against age/weight ratios and compared to that predicted from the preliminary dose-response curve.

RESULTS

In the 17 patients, 15 to 75 years of age, studied, the desired level of hypotension was attained and maintained without difficulty. The MAP during hypotension in the study group was 65 ± 4 torr.† Once the desired level of blood pressure was reached, only minor changes in the rate of infusion were required to maintain constant levels of hypotension. As a result, the calculated average minute dose of NP (μg/min) differed little from the actual minute-to-minute dose resulting from minor fluctuations in pressure.

The action of NP began within 60 to 90 seconds after starting the infusion and the duration of action was short when the infusion was stopped. Blood pressure began to rise toward normal within 120 seconds after infusion ended. Blood pressure decreased in proportion to the amount of NP infused; however, no correlation was found between the minute dosage of NP required to lower the blood pressure of a given patient to comparable levels in a group of patients of similar weight. This finding confirms the results noted in our earlier study (fig 2).

An inverse relationship between patient age and minute dosage was again noted, but the correlation was not statistically significant (fig 3). When the required dose of NP was plotted against the age/weight ratio of each study patient, a highly significant relationship could be seen. The curve derived from this study did not differ significantly from that of the previous study. The combined data from the 30 patients in the 2 studies (fig 4) gave a better statistical fit ($p<0.001$, $r = -0.8939$) than that found in the preliminary study alone.

The duration of deliberate hypotension for the 17 patients averaged 90 (± 15) minutes. Acid-base balance remained normal and no tendency toward acidosis was noted. Actual operating time averaged 110 ± 15 minutes. The average blood loss in the study patients was 450 ml (± 100) compared with 1480 ml (± 200) in 10 patients receiving total hip replacement under normotensive anesthesia by the same surgical team.

Transfusion was required in only 2 of the 30 study patients, each receiving 2 units. Both patients had had multiple operations on the involved hip, and the transfusion was required as a result of posthypotensive blood loss. In comparison, a total of 23 units of homologous blood was given to the 10 control patients, who were kept normotensive. When no blood was given during or after operation, the hemoglobin count declined slowly until the 3rd postoperative day. The lowest postoperative hemoglobin noted in the study was 8.8 gm/100 ml in a Jehovah's Witness patient. No adverse effects were seen as a result of SNP-induced hypotension.

*Harvard Apparatus Company, Millis, Massachusetts.

†Mean value refers to the arithmetic mean.

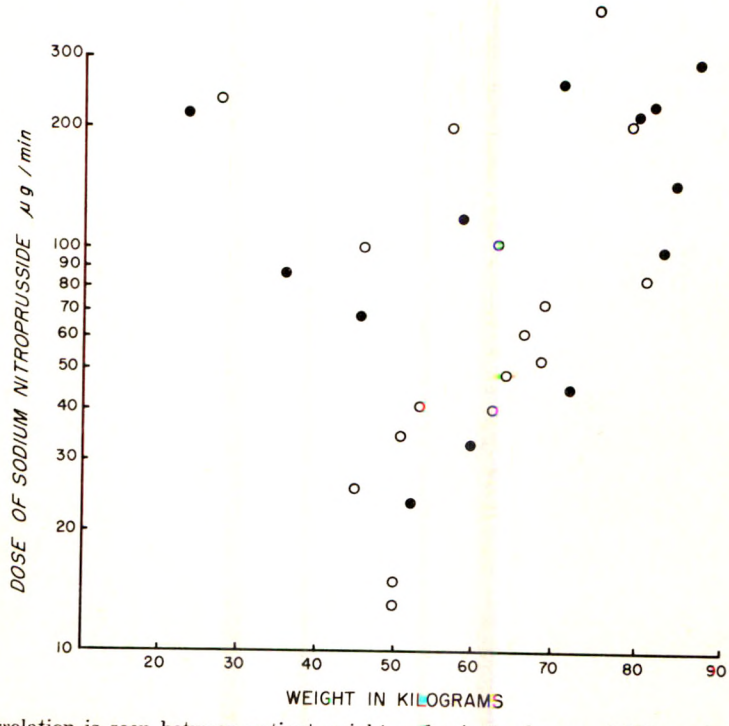


FIG 2. No correlation is seen between patient weight and minute dosage of NP needed for comparable levels of hypotension. Preliminary study[10] data (solid circles) are compared with present study data (open circles).

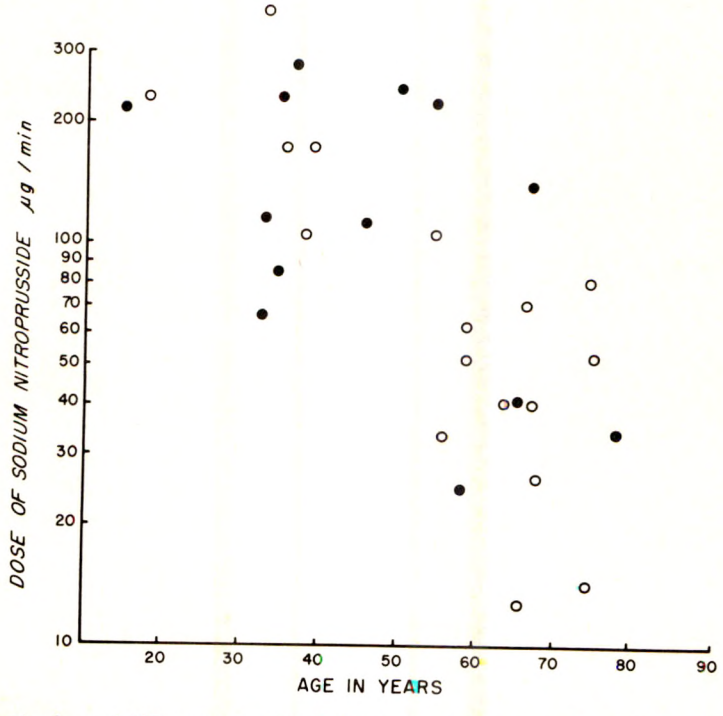


FIG 3. The minute dose of NP appears related inversely to the age of the patients but the relationship was not statistically significant. Preliminary study[10] data (solid circles are compared with present study data (open circles).

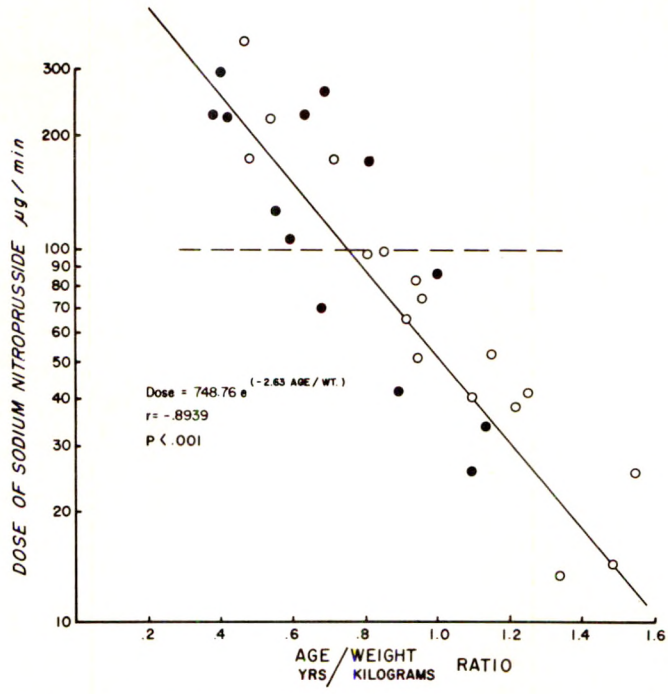


FIG 4. Age/weight ratios (yr/kg) produce a highly significant dose-response curve relating the minute doses of NP needed to produce comparable levels of hypotension in a given patient population. The combined data of the preliminary study[10] (solid circles) and the present study (open circles) produce a better statistical fit than does the original curve (fig 1). A concentrated solution (100 µg/ml) is used when predicted dosage is above 100 µg/min.

DISCUSSION

The safety of NP has been ascribed[6-9] not only to its improvement of tissue perfusion during hypotension but also to the evanescence of its action. The speed of onset and duration of action of NP is between 60 to 120 seconds, necessitating a continuous infusion to maintain constant levels of hypotension. The magnitude of the blood pressure response is dose dependent, and pressure levels can be changed within seconds, if needed, by altering the infusion rate. In the past, this speed of action, coupled with an apparent variation of potency and dose in a given patient population of similar body weights, has constituted one of the main difficulties in NP administration.

Previously, NP dosage had to be adjusted empirically according to response, recommended dosage ranging from 0.5 to 30 µg/kg/min.[7] Our experience with 30 patients has confirmed this wide range of doses based on weight. The dosage of NP required to produce comparable levels of hypotension within a group of patients of similar body weight is entirely unpredictable (fig 2). An inverse relationship between age and required dose was more apparent, but this correlation was not statistically significant either (fig 3). However, when both age *and* weight were considered (age/weight ratios), a highly significant dose-response relationship resulted (fig 4).

A nomogram relating the age/weight ratio to infusion rate has proven to be of considerable practical value in our hands. It has eliminated the time-consuming and often dangerous empirical search for the NP dose required to produce consistently safe levels of hypotension in a given patient. Thus, the nomogram represents an additional margin of safety in the use of this potent and fast-acting drug.

Taylor's group[9] and Davies and coworkers[11] have noted that young patients require larger doses of NP than do adults to produce the same degree of hypotension. A review of the nomogram confirms that observation. The age/weight ratio of a normally developing child from age 2 years until maturity remains relatively constant at between 0.3 and 0.5. Ratios in this range on the curve would indicate that the required NP dosage under halothane anesthesia would be in the range of 200 to 300 µg/min throughout

childhood and adolescence. However, the relationship between age, weight, and dosage remains constant over a wide range of ages. For example, a 38-year-old patient from the current study weighed 98 kg, for an age/weight ratio of 0.35. He required 275 μg/min of NP to produce and maintain a MAP of 65 torr. Likewise, a 9-year-old patient in the previous study, weighing 24 kg (age/weight ratio = 0.38) required 230 μg/min to produce a comparable level of hypotension. On a weight basis, the 9-year-old received 9.6 μg/kg/min as compared to 2.3 μg/kg/min for the 38-year-old.

Doubts have been expressed about the safety of NP, particularly in children,[11,12] because its immediate metabolic products are cyanide and thiocyanate. Vesey's group[13] reported a significant rise in plasma cyanide following the infusion of NP for hypotensive anesthesia. They concluded, however, that those levels encountered did not produce toxic effects. Recently, several anesthetic deaths[12,14,15] have been reported in which NP was implicated, but most of these occurred under extraordinary circumstances in which the evidence against NP may be spurious. Only Davies and colleagues[12] clearly documented a death due to NP overdose. Johnson[4] described the therapeutic index of NP to be around 10:1, but McDowell's group,[16] working with primates, suggested that the ratio might be closer to 6:1. Also, the concentration of accumulated toxic byproducts is related obviously not only to the total dose given but also to the time over which it is administered.[17] Certainly, NP has been safely used for extended periods in treating hypertensive crises without a dangerous build-up of toxicity.[3] The fatality reported by Davies involved 120 μg/kg/min (4800 μg/min) of NP given over 80 minutes. This patient's age/weight ratio was 0.35 and he thus received 20 times the dose the nomogram would have predicted. Davies attributed this large dose to tachyphylaxis, a phenomenon not observed in our series, even in the young.

The question of tachyphylaxis requires comment. Autonomic nervous system responses, especially sympathetic, during anesthesia and operation, are a function of the depth of anesthesia, as well as of body temperature, hypoxia, respiration, and acid-base balance. In these circumstances, an increase in sympathetic vasoconstrictor activity or heart rate may result. To overcome this active sympathetic effect, an increasing infusion rate of NP will be needed to maintain constant levels of hypotension against the efforts of the homeostatic system.

In our experience, the so-called tachyphylaxis to the drug during anesthesia, requiring doses greater than that predicted, has served as a warning of unattended sympathetic compensation secondary to physiologic alterations, rather than true tachyphylaxis. Correction of a temperature deficit, inadequate anesthesia, hypoxia, or acidosis has always reduced the NP requirement. The fatal case reported by Davies[12] exhibited a marked but compensated metabolic acidosis (base deficit = −9) before the NP was administered. The possibility of a metabolic defect was not excluded. Equally, the other fatal reports in which NP has been implicated included severe physiologic alterations such as hypothermia[14] (31° C body temperature), airway obstruction, hypoxia,[15] and/or acidosis.

We have found SNP to be safe, effective, and predictable in reducing blood pressure and surgical blood loss in selected patients undergoing total hip replacement in the supine position. The effects of drugs or anesthetic technics, other than those described, on the slope or position of the NP dose-response curve remain to be explored.

REFERENCES

1. Larson AG: Deliberate hypotension. Anesthesiology 25:682-706, 1964

2. Guiha NH, Cohn JN, Mikulic E, et al: Treatment of refracting heart failure with infusion of nitroprusside. N Engl J Med 291:587-592, 1974

3. Gifford RW: Hypertensive emergencies and their treatment. Med Clin North Am 45:441-452, 1961

4. Johnson CC: The actions and toxicity of sodium nitroprusside. Arch Int Pharmacodyn Ther 35:480-496, 1929

5. Moraca PO, Bitte EM, Hale DE, et al: Clinical evaluation of sodium nitroprusside as a hypotensive agent. Anesthesiology 23:193-199, 1962

6. Ross G, Cole PV: Cardiovascular actions of sodium nitroprusside in dogs. Anaesthesia 28:400-406, 1973

7. Styles M, Coleman AJ, Leary WP: Some hemodynamic effects of sodium nitroprusside. Anesthesiology 38:173-177, 1973

8. Wildsmith JAW, Marshall RL, Johnson JL, et al: Haemodynamic effect of sodium nitroprusside during nitrous oxide-halothane anaesthesia. Br J Anaesth 45:71-74, 1973

9. Taylor TH, Styles M, Lammins AJ: Sodium nitroprusside as a hypotensive agent in general anaesthesia. Br J Anaesth 42:859-893, 1970

10. Lawson NW, Thompson DS, Nelson CL, et al: Sodium nitroprusside-induced hypotension for total hip replacement. Anesth & Analg (in press)

11. Davies DW, Greiss L, Kadar D, et al: Sodium nitroprusside in children: observation of metabolism

during normal and above responses. Can Anaesth Soc J 22:553-560, 1975

12. Davies DW, Kadar D, Steward DJ, et al: A sudden death, associated with the use of soduim nitroprusside for induction of hypotension during anaesthesia. Can Anaesth Soc J 22:547-552, 1975

13. Vesey CJ, Cole PV, Linnel JC, et al: Some metabolic effects of sodium nitroprusside in man. Br Med J 2:140-142, 1974

14. Merrifield AJ, Blundell MP: Toxicity of sodium nitroprusside. Br. J Anaesth 46:324, 1974

15. Jack RD: Toxicity of sodium nitroprusside. Br J Anaesth 46:952, 1974

16. McDowell DG, Keaney NP, Turned JM, et al: The toxicity of sodium nitroprusside. Br J Anaesth 46:327-332, 1974

17. Vesey CJ, Cole PV: Nitroprusside and cyanide. Br J Anaesth 47:1115, 1975

Guest Discussion

ROBERT K. STOELTING, MD
Department of Anesthesia
Indiana University Medical School
Indianapolis, Indiana

Dr. Lawson and coworkers have demonstrated that the age/weight ratio correlates with the minute dose of sodium nitroprusside (SNP) necessary to reduce the blood pressure to about 65 torr. Accordingly, my discussion will deal with those characteristics that may influence SNP dose requirements.

Factors that should be considered in determining the dose of any drug include body weight, patient age and physical condition, route of drug administration, hepatic and renal function. Unique to the SNP dose requirements one should also consider the blood pressure prior to drug administration, the desired magnitude of blood pressure reduction, and the influence of any concomitantly administered drugs, such as anesthetics.

Body weight (and body surface area) reflect the volume of drug distribution, which may be different in thin versus obese or in dehydrated versus edematous patients. The relative volume of body fluid compartments may vary with age and be influenced by serum protein concentrations. Recently, Koltz and associates[1] reported that the elimination, or beta half-life, of diazepam increased in direct proportion to patient age, due to increased drug distribution volume.

The maintenance of a constant drug concentration during steady-state infusion, as with SNP, is determined by the rate of biotransformation as reflected by the drug half-life and the volume of drug distribution in the body.[2] The hypotensive effect of SNP is due to the nitroso portion of the free drug.[3] The evanescent response reflects the drug's rapid breakdown to products lacking vasodilating properties.[4] This breakdown occurs in 2 steps: First, there is a nonenzymatic reaction of the iron atom with sulfhydral groups (primarily in the erythrocytes) to form cyanide. Second, cyanide is converted to thiocyanate by the hepatic enzyme, rhodanase.

Whether underlying hepatic disease or enzyme induction would influence the rate of SNP biotransformation is not established. Conceivably, altered rates of biotransformation might result in different blood-pressure effects from the same minute dose of SNP, since more or less drug would remain in the active form. However, liver function is probably unimportant in determining the SNP dose, since the initial drug breakdown is not enzyme dependent. Likewise, the initial nonenzymatic biotransformation would suggest that decreased drug delivery to the liver, secondary to anesthetic-produced reductions in hepatic blood flow, would not influence the SNP dose necessary to reduce blood pressure.

Little is known about protein binding or tissue and blood solubility of SNP and how these factors might influence the distribution volume of the drug. Even were these known, the adjustment of dosage on the basis of pharmacokinetic principles is only an approximation, with the final maintenance dose determined by patient response.

I would like to ask Dr. Lawson the following questions:

1. Why did the age/weight ratio correlate with the minute dose of SNP when neither variable alone produced a similar correlation?

2. How does one adjust the dosage nomogram at the extremes of body weight or fluid balance?

3. Would the dosage nomogram be similar in hypertensive versus normotensive patients or with similar control blood pressures but different anesthetic maintenance drugs (halothane-N_2O versus fentanyl-N_2O)?

REFERENCES

1. Koltz U, Avant GR, Hoyumpa A, et al: The effects of age and liver disease on the disposition and elimination of diazepam in adult man. J Clin Invest 55:347-359, 1975

2. Greenblatt DJ, Koch-Weser J: Clinical pharmacokinetics. N Engl J Med 293:964-970, 1975

3. Johnson CC: The actions and toxicity of sodium nitroprusside. Arch Int Pharmacodyn Ther 35:480-496, 1929

4. Page IH, Corcoran AC, Dustan HP, et al: Cardiovascular actions of sodium nitroprusside in animals and hypertensive patients. Circulation 11: 188-198, 1955

Addendum

ANSWERS TO DR. STOELTING'S QUESTIONS:

1. Why did the age/weight ratio correlate with the minute dose of SNP when neither variable alone produced a similar correlation?

Examination of the graphs relating dose to age *or* weight suggests that the minute dose of SNP required to produce comparable levels of hypotension in a group of patients is inversely related to age but directly proportional to weight. However, neither factor alone correlated sufficiently to be clinically useful in predicting dose-response. Age and weight appeared to have counteracting effects in dose-response, each modifying the other, but to different degrees. We examined weight/age ratios, age/weight ratios, and body surface area in relation to the dose requirements. Weight/age ratios did not produce a mirror image of the age/weight ratio response but *was* statistically significant ($p<0.01$). Age/weight ratios produced a more significant response ($p<0.001$). Thus age, when used as the numerator in the ratio, appeared to be the more important factor in determining dose, although the relationship is inverse. Weight (mass) modifies the age dose-response by determining the volume to which the drug was distributed. Statistically, body surface area fared no better than weight alone in predicting dose-response.

Clinically, age is perhaps an indirect assessment of metabolic rate (biotransformation) which also varies inversely with age. Too, age might relate indirectly to changes of vessel compliance with age. I feel that the use of age and weight to determine the dose response of SNP is a useful clinical tool. One might produce a more accurate dose-response curve if it were clinically feasible to determine metabolic rate and body surface area in the everyday practice of anesthesia.

2. How does one adjust the dosage nomogram at the extremes of body weight or fluid balance?

Our study was performed on carefully selected patients who were otherwise healthy except for their hip disease. Criteria for hip replacement ruled out the selection of obese patients. We have administered SNP to several obese patients for other procedures. The minute dose for these patients, in retrospect, was predictable on the proposed nomogram when their weight, used in the age/weight ratio, was corrected to their ideal weight according to life insurance tables. They took less than predicted if their actual weight were used in determining dosage. Thus, adipose tissue remains a "slow space" for nitroprusside as well as other agents used in anesthesia.

We have not had any experience with nitroprusside in patients at the extremes of fluid balance. Patients, under these conditions, thus far, are not candidates for hypotensive anesthesia.

3. Would the dosage nomogram be similar in hypertensive versus normotensive patients or with similar control blood pressure but different anesthetic maintenance drugs (halothane-N_2O versus fentanyl-N_2O)?

Patients with renal hypertension are not candidates for deliberate hypotension during anesthesia but nitroprusside may be used to control hypertension during surgery on these patients. We have administered nitroprusside to 7 patients with controlled essential hypertension for hypotensive anesthesia exclusive of the present report. The dose-response fell within the statistical range predicted by our nomogram. However, there have not been enough patients of this type to determine if their dose-response curve might be shifted from the norm for their particular condition. Schlant and coworkers[1] noted in 1962 that patients with hypertension appeared more sensitive to the effects of nitroprusside. However, we have since recognized that uncontrolled hypertensive patients also have a reduced plasma volume. Volume depletion might accentuate the effects of vasodilatation rather than be representative of a true hypersensitivity to SNP. We have not explored the effects of other anesthetic agents on the slope or position of the SNP dose response curve.

REFERENCE

1. Schlant RC, Tsagaris TS, Robertson RJ: Studies on the acute cardiovascular effects of intravenous sodium nitroprusside. Am J Cardiol 9:51-59, 1963

"An' Ho, Ho, Baby, Take a Whiff on Me:" La Dama Blanca Cocaine in Current Perspective

GEORGE R. GAY, MD, AACT, FAAFP*
DARRYL S. INABA, Pharm D†
RICHARD TOBIN RAPPOLT, SR., MD, ABMT‡
GEORGE F. GUSHUE, JR., DO§
JOHN JAMES PERKNER, DO‖

A CLASSIC drug of antiquity,[1] cocaine, the active alkaloid of the shrub *erythroxylon coca,* is perhaps the most exquisitely euphorogenic as well as the most monumentally illegal drug of all time.[2] In the drug-using counterculture, a remarkable upsurge in popular illicit use of cocaine was witnessed in mid-1970, reaching a plateau by mid-1972.‖[3] It is our purpose to offer a practical clinical review of the treatment of acute and chronic cocaine overdose (OD), along with some of the rich background history of this drug.

"The Dreadful Andes plac'd twixt Winter's Store of the Winds, Rains, Snow, and that more humble Earth, That gives the small, but valiant, Coca birth."
Abraham Cowley (1721)[1]

The coca leaf was believed to be a gift to the Inca people from Manco Ccapac, son of the Sun God, bestowed as a token of esteem and sympathy for their suffering labor. The leaves were initially to achieve a rather narrow usage among the religious and political aristocracies of the Inca society; a much broader and perhaps more sinister pattern was noted following the destruction of the Incan civilization in the 16th century by Francisco Pizzaro and the invading conquistadores, as the lower classes and slaves were "paid off" in coca leaves as an effective method of increasing and and prolonging low-cost, high-output labor. In practice, coca leaves, bound into a ball (or *cocada*) with guano or cornstarch, were chewed with lime (as alkaline ash) to release the active alkaloid.

Thus coca served as a stimulating tonic to those working in the thin air of the Andes. Further, anthropologic documentation indicates that the highly sophisticated surgical procedure of trephination was repeatedly successful in this era, as the operating surgeon allowed coca-drenched saliva to drip from his mouth onto the surgical wound, thus providing adequate (and very real) local anesthesia, and permitting the operation to proceed in relative quiet.*

Little was heard of coca as a medical entity until 1859, when the Italian physician, Paolo Mantegazza, declared coca leaves to be a "new and exciting weapon against disease;" his narrative, however, cannot be regarded as objective scientific observation, as he wrote:

‖Greater than 50% of a recent random sample of clients at the Haight-Asbury Free Medical Clinics reported use of the agent "at least once during the past 2 months."

*Such surgically incised skulls, along with pottery shards depicting faces with cheeks stuffed with coca leaves, have been dated back some 1200 years.

*Former Director of Clinical Activities, Haight-Ashbury Free Medical Clinics, San Francisco, California. Present address: P.O. Box 1169, Mendocino, California 95460.

†Director of Pharmaceutical Services, Haight-Ashbury Free Medical Clinics, San Francisco, California.

‡Editor, CLINICAL TOXICOLOGY, 4141 Geary, Suite 403, San Francisco, California.

§Preceptee, Family Practice Program, Mendocino, California.

‖Preceptee, Family Practice Program, Mendocino, California.

Paper received: 9/9/75

Accepted for publication: 3/31/76

Portions reprinted with permission from Marcel Dekker, Inc., New York, New York and the authors.

"Borne on the wings of two Coca leaves, I flew about in the spaces of 77,438 worlds, one more splendid than another. . . . It seemed to me that I was separated from the whole world, and I beheld the strangest images most beautiful in color and in form than can be imagined."

In England, meanwhile, coca leaves were being viewed as a pharmacologic curiosity, while American physicians echoed Mantegazza, heralding the drug as a cure-all for almost every recognized malady, including alcoholism, tuberculosis, opiate addiction, and heart failure.

Alfred Neimann isolated the coca alkaloid in 1860 and named it "cocaine." By 1865, preparations of coca leaves and wine were introduced onto the open market, the classic example being "Vin Mariani." A true advertising genius, Angelo Mariani received public testimonials to his tonic from such dignitaries as Queen Victoria, Pope Leo XIII, Sarah Bernhardt, and Thomas Edison (Mariani's company published these in a series of 12 volumes), and he may have come closer to "turning on the world" than any man in history.[4]

The coca boom was soon to follow in Europe, when in 1884, a cocaine "kit" from Eli Merck was delivered to Dr. Sigmund Freud in Vienna. Ever the visionary experimenter, Freud was shortly using coca in the treatment of various medical and psychologic disorders. Between 1884 and 1887, he wrote five papers ("Über Coca") extolling coca as a wonder drug, but his "coca euphoria" subsided abruptly and he subsequently deleted these laudatory writings from the collected papers of his autobiography.

Simultaneous with Freud's enthusiastic pronouncements, his own colleague. Dr. Karl Koller, delivered a formal paper before a prestigious group of ophthalmologists on the potent local anesthetic effects of cocaine upon the corneal nerve endings, and was subsequently praised by Freud as the "true discoverer" of anesthesia.

The introduction of cocaine as a local anesthetic created enormous new opportunities for surgical anesthesia, and Dr. William Halsted, of Johns Hopkins in Baltimore, performed the first "nerve blocks" in 1885.[5] (By 1886, Halsted was to write no further about cocaine as he battled his own 2 gm/day habit.) Coca Cola®, the first of the popular proprietary cocaine-containing "soft drinks," was introduced by Asa G. Candler in 1888, and in the ensuing years countless cocainized over-the-counter nostrums flourished. In the surgical amphitheater circa 1899, cocaine had been employed as a successful "spinal anesthetic" by Drs. Tait and Cagliari of San Francisco and Dr. Rudolph Matas of New Orleans.

In 1906, the Pure Food and Drug Act was passed, legislating the mandatory labelling of all proprietary medications. This marked the end of the cocaine-Coca-Cola alliance, but it was not until the Harrison Tax Act of 1914 that cocaine was legally (although pharmacologically inaccurately) defined as a "narcotic;" and, with all semblance of quality control removed, its use disappeared underground.

Except for a small (and diminishing) recognized use of cocaine in strictly medical settings, it has existed since that time as a black-market commodity. Over the ensuing 62 years its presence has been noted among suppressed inner-city populations, various enclaves of American music culture, the affluent, and the artistic "bohemian" culture.

Take a Whiff on Me

Blacker de berry, de sweeter de juice,
Takes a brown-skin woman for my partickler use
An' ho, ho, baby, take a whiff on me.
Chew my 'baccer, spit my juice,
Gonna love my baby, 'till it ain't no use
An' ho, ho, baby, take a whiff on me.
Whiffaree an' a whiffarye,
Gonna keep on a-whiffin' until I die,
An' ho, ho, baby, take a whiff on me.
Cocaine for horses an' not for men,
Doctors say it'll kill you but they don't say when
An' ho, ho, baby, take a whiff on me.
Leadbelly (1933)

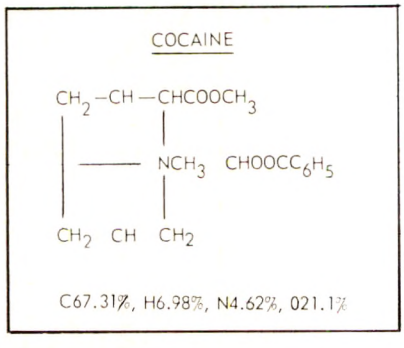
An aura of mystic romanticism has enshrouded cocaine throughout its history. Robert Louis Stevenson is said to have composed the 1st draft of "Dr. Jekyll and Mr. Hyde" in 3 days while undergoing treatment of tuberculosis with cocaine. Arthur Conan Doyle, the literary genius who created the sleuth who was to become the epitome of cold, crystalline logic, opened his novel, *The Sign of Four*:

"Sherlock Holmes took his bottle from the corner of the mantelpiece, and his hypodermic syringe from its neat morocco case. . . . 'It is cocaine,' he said, 'a seven-percent solution. Would you care to try it?' "

Presently the coca leaf is cultivated legally in only 2 countries, Peru and Bolivia, where is produced the majority of the world's supply. After each harvest in March, June, and November, a complex exportation process ensues, the product being smuggled across various borders either in leaf form or as a raw paste extracted by kerosene, with varying degrees of sophisticated refining carried out en route.* From coastal debarkation ports, cocaine eventually finds its way to a broad world market, with North America and Europe serving as its major consumers.

In recognized street jargon, the feminine gender ("Her," "Lady," "La Dama Blanca," "Girl") is used synonymously for cocaine; other popular nicknames ("Happy Trails," "Nose Candy," "The Star Spangled Powder," "Snow," "Flake," "Heaven Leaf," "The Rich Man's Drug," "The Pimp's Drug") describe aspects of the agent's appearance and hint at some of cocaine's fascinating sociologic facets.

The Chemistry and Pharmacology of Cocaine.—Chemically, cocaine is benzoylmethylecgonine with the empiric formula $C_{17}H_{21}NO_4$.



Cocaine, the only naturally occurring local anesthetic, is an ester of benzoic acid and the nitrogen-containing base, ecgonine. On hydrolysis, it yields benzoic acid, methyl alcohol, and the tropine derivative, ecgonine.[6] It exists as a fairly stable, white crystalline compound; its hydrochloride salt dissolves in ½ its own weight in water.

Pharmacologically, cocaine exhibits a distinct duality of action: it is a local anesthetic of high efficacy (and also high toxicity), and a potent systemic CNS stimulator. This latter effect is noted from above downward, the first recognizable effects being cortical.

As for the autonomic nervous system, cocaine potentiates adrenergic receptor site organs and slows the uptake of both endogenous and exogenous catecholamines. Cocaine markedly contributes to systemic heat production and retention through a greatly increased somatic activity despite concurrent vasoconstriction. In legitimate medical use, cocaine continues to enjoy a popularity as the topical anesthetic nonpareil, although its high toxicity, "bad press," and DEA red-tape have led many physicians to turn to the less efficacious but much more readily available alternative of lidocaine.

"Lady of the Street."—In the current drug subculture, cocaine remains the "champagne of drugs." The experienced "cokehead" considers himself to represent the aristocracy of drug-users. Enormously inflated on the illicit market, an ounce of "coke" may be purchased for from $500 to over $1500, $50 to $100 a gram, or $10 a "line" or "snort" of up to 200 mg of "material." (Ask, but don't buy from, any cab driver in Mexico City.) All of this for what may have been "stepped-on" by various intermediary entrepreneurs, and may represent 25 to 80% quinine (for a better taste), lidocaine crystals (for the "freeze"), plus a little amphetamine (for the "rush"). Pure wholesale cocaine sells to medical institutions, on the other hand, for about $20 an ounce.

As coke has entered the drug-using consciousness of white middle-America, the earlier historical pattern of IV injection has now been largely supplanted (in a righteously needle-fearing society) by the inhalation route, in which a "line" of coke is "horned," "snarfed," or "snorted," often through a Federal Reserve note of high denomination (to denote affluence) or through a red, white, and blue sipping straw.

A complication from this method of administration is septal perforation, due to intense and repeated vasoconstriction. Snorters are also prone to infection of the nasal mucosa and upper respiratory tract, due to chronic local irritation. This may further lead to several days to a week of sneezing and (pseudo) coryza-like symptoms following an evening with "La Dama Blanca." In addition, reactive hyperemia following a coke-spree leads to boggy mucosa and a chronic stuffy nose (Afrin® is a favorite relief). Thus the coke-head's dyad is seen, of

*One hundred kg of coca leaves yields approximately 1 kg of refined cocaine.

(a) the paraphernalia (silver spoon or straw on a necklace, or a snuffbox) and (b) the ever-present nasal spray. The cocaine user is truly protected by the limitations of his own pocketbook and of his nasal mucosa.

Cocaine must be recognized as *the* ultimate euphorogenic (and in high doses, hallucinatory) drug available on the street today. Its preference by the drug connoisseur is undisputed. Cocaine tends to enlarge and glorify the entire world of the user. It also further continues to enjoy the reputation as the "primo" enhancer of sexual activity. Coke is used in sexual situations, not only via the inhalation and IV routes but also by being rubbed directly onto the genitalia, thereby producing partial anesthetization and a tingling sensation.[7] In the physically/pharmacologically exhaused individual, however, cocaine may have definite inhibitory effects on sexual performance, particularly in regard to male potency.

Caveat emptor! A practical street method of bioassay of coke is to (1) fill a dark glass receptacle with Clorox® (sodium hypochlorite) and (2) drop a pinch of the alleged substance ("neat," ie, uncut) into the middle of the Clorox pool. If the buyer has not been "burned" by a bogus product, he will note the initial white color turning to a greenish blue halo with the pinch plummeting to the bottom. (Many other chromophores will give a similar reaction.) The classic street test remains the "straight snort;" if the front incisors and canine teeth are numb after a "test line," it is presumptive positive evidence of "The Real Thing."[3]

Cocaine Overdose and Treatment.—Even with small doses of cocaine, an increase in blood pressure and pulse rate is initially seen.[8] If OD occurs, the victim may first report mental depression, dry throat, and dizziness. He/she may express a sudden overwhelming desire to defecate or micturate, in a spasm of smooth-muscle tonus. Sweating, confusion, and vomiting are noted as the central sympathetic onslaught continues.

An unhappy effect of a few milligrams too many is a paradoxic respiratory depression following an initial increase in rate and depth. A rapid, shallow pattern may ensue, Cheyne-Stokes may appear, and death may occur due to central respiratory collapse. Further, intense vasoconstriction combined with hypermetabolism may lead to hyperpyrexia; hyperreflexia, CNS anoxia, and tonic-clonic convulsions may supervene. A CNS "bleed" may occur. Ventricular fibrillation or direct cardiac standstill, even with doses as low as 30 mg, has been reported. Individual variability, and possible anaphylactoid sensitivity to cocaine, further narrow the discernable safety margins.

The standard fatal dose of coke is considered to be 1.2 gm (in a 70-kg man), with the LD_{50} being 500 mg. This may prove misleading, as these figures were derived from oral dosage; it must be recalled that cocaine is rapidly hydrolyzed in the stomach and thus largely inactivated. It has been estimated that the liver can detoxify 1 minimal lethal dose of coke per hour. An extrapolation from the larger doses given above would translate to 10 gm/day, if taken in incremental doses! (Neither true physical dependence nor tolerance — either to its pleasurable or toxic effects—occurs, and fortunately for the casual user, the 10 gm/day figure translates in street economy to a staggering $500 to $1000.)

Prolonged or chronic use of cocaine may lead to an irrational affect not unlike paranoid schizophrenia. Plagued with the dark shadows of increasing nervousness, inability to concentrate, and disturbed sleep patterns, the chronic user is increasingly prone to violence.[9] Due to these paranoia-producing qualities, and coupled with the very real heavy legal sanctions involved in the possession/use of cocaine, the user will seldom be seen in your office or in emergency rooms of traditional medical facilities. More often, in an attempt to "come down," he will self-medicate with a combination of alcohol, barbiturates, "Soapers," heroin, and/or other sedative-hypnotics (which further muddies the water, when— and if— you are called to treat him). If, however, panic or the true acute crisis of cardiac or respiratory collapse following cocaine use brings such an individual to your door—in *all* cases, acute or chronic—the treatment is symptomatic, and should remain flexible and dynamic.

In cases of acute toxicity, death most often occurs within 2 to 3 minutes, but may occur up to 30 minutes following ingestion/injection. If the acute OD victim survives the first 3 hours, his chances of recovery are almost certain.

Remember the biphasic nature of the "caine reaction," with initial sympathetic stimulation, followed by abrupt generalized CNS depression (at all levels). It thus follows that he who would administer first aid must first determine just which phase of

A CHRONOLOGY OF COCAINE

9th Century AD	Pre-Incan period. Coca leaves found in graves in the Central Amazon.
1200-1553	Inca Empire. Coca declared gift of Sun God; a divine plant.
10th-12th Century	Tombs, Andes region, containing trephined skulls. Juice from coca leaves believed used for local anesthesia.
1553	Francisco Pizarro and followers "paid off" workers in coca leaves, hastening destruction of Incan civilization.
1569	Increase in coca leaf chewing by lower classes of Andean Indians reported by Nicholas Monardes.
1580	Monardes brings coca leaves to Europe.
1853	Dr. Alexander Wood of Edinburgh invented the hypodermic syringe.
1853	Charles-Gabriel Pravaz, of Lyon, France, added an improved needle to the syringe.
1855	Gaedicke, of Germany, isolated an alkaloid of the leaves of the coca plant, naming it "erythroxylon."
1859	Dr. Paolo Mantegazza, of Italy, declared coca leaves a great new weapon against disease.
1860	Alfred Niemann purified the coca alkaloid and named it "cocaine," also noting its numbing effect on the tongue.
1865	"Vin Mariani," a preparation of wine and coca leaves, introduced to open market.
1873	Alexander Bennett demonstrated the anesthetic properties of cocaine.
1878	Vasili Konstantinovich von Anrep thoroughly studied the pharmacologic properties of cocaine, partly by injecting the skin of his own arm. He suggested the use of cocaine as an anesthetic agent.
1884	Karl Koller (an associate of Freud), at Vienna General Hospital, introduced cocaine into medical practice as a local anesthetic for eye operations.
1884-1887	"Ueber Coca:" Sigmund Freud wrote 5 enthusiastic papers extolling the virtues of coca and cocaine.
1884-1885	"The Great Cocaine Explosion:" Cocaine a fad overnight. Merck and Company and Parke-Davis and Company entered commercial field.
1884	Dr. William Halsted, of Johns Hopkins, injected cocaine into nerve trunks, obtaining "nerve block" or "conduction" anesthesia.
1885	Dr. James Leonard Corning, of New York, suggested use of cocaine for spinal anesthesia.
1888	Asa G. Candler introduced Coca-Cola as a "tonic for elderly people who were easily tired." First (and most successful) or proprietary cocaine-containing "colas." The soda fountain becomes a part of Americana.
1897	Dr. George W. Crile, of Cleveland, used direct infiltration of nerve trunks with cocaine for amputation. Dr. Harvey Cushing, of Johns Hopkins, performed a herniorrhaphy using a similar technic.
1898	August Bier, of Griefswald, Germany, obtained true spinal anesthesia—injecting animals, an assistant, and *himself* with cocaine (a paraplegic circus).
1898-1899	Drs. Tait and Cagliari, of San Francisco, and Dr. Rudolph Matas, of New Orleans, used cocaine for spinal anesthesia in surgical procedures.
1902	Richard Willstätter synthesized cocaine.
1902	Survey by Crothers showed only 3 to 8% of the cocaine sold in New York, Boston, and other metropolitan areas went into the practice of medicine or dentistry.
1906	Pure Food and Drug Act: Required accurate labelling on all over-the-counter preparations.
1914	Harrison ("Narcotics") Tax Act: Persons authorized to handle or manufacture drugs required to register, pay a fee, and keep a record of all "narcotics" (including cocaine) in their possession.
1914-1970	Cocaine underground. Used by "bohemians," "go-go girls," "gypsies" (chorus boys and girls), "jazz," "beat," "country and western," and "rock" music cultures. Also, highly esteemed in prisons and depressed ghettos for its euphoric properties.
1970-present	Reemergence in white "middle-America" of cocaine as illicit drug of preference.
1975	Cocaine named by "Rolling Stone" magazine as "Drug of the Year . . . Again!"

the cycle he is witnessing. The present authors have noted in a series of over 50 cases the beneficial response to use of the beta blocker, propranolol, in reversing the immediate sympathomimetic effects of cocaine.* In the presence of frank convulsions, incremental doses of the ultrashort-acting barbiturates (thiopental), given IV in doses of 25 to 50 mg, have proven beneficial (but always beware of potentiating CNS anoxia; don't "dose a dose").

In the presence of the chronic user who is restless, sleepless, and paranoid, the benzodiazepines (almost *never* the phenothiazines) in 1.5 normal dosage, either PO, IM, or IV, have proven of great efficacy. In *every* case, consider the patient as one large, raw nerve endplate. Approach with the science of "ART" (Acceptance; Rest and Reassurance; Talkdown Technic).

Keep cool; keep the patient cool (ice for hyperpyrexia is good). If you can convince this patient that you are a physician and not a policeman, then the both of you may survive.

*Propranolol is given in 1-mg increments IV at 1-minute intervals, up to 8 mg total. Heart rate and general metabolic status will return to normal limits within 1 to 3 minutes. The centrally acting emetic effect of cocaine will not be obtunded, however.

REFERENCES

1. Mortimer WG: History of Coca. "The Divine Plant" of the Incas. San Francisco, AND/OR Press, 1974

2. The Gourmet Cokebook. White Mountain Press, 1972

3. Gay GR, Inaba DS, Sheppard CW, et al: Cocaine: History, epidemiology, human pharmacology and treatment. A perspective on a new debut for an old girl. Cocaine in perspective. Clin Toxicol 8:149-177, 1975

4. Mariani A: Coca and Its Therapeutic Application. New York, JN Jaros, 1896

5. Keys TE: The History of Surgical Anesthesia. New York, Dover Publications, Inc, 1963

6. Jaffe JH: Drug addiction and drug abuse. The Pharmacological Basis of Therapeutics. Fifth edition. Edited by LS Goodman, A Gilman. New York, The Macmillan Company, 1975, pp 379-403

7. Gay GR, Sheppard CW: Sex-crazed dope fiends–myth or reality. Proceedings of the National Academy of Science, Meeting on Drug Dependency, May, 1972

8. Dimijian G, Radelat F: Evaluation and treatment of the suspected drug user in the emergency room. Arch Intern Med 125:162-170, 1970

9. Final Report of the Commission of Inquiry into the Non-Medical Use of Drugs, *LeDain Commission*. Ottawa, Crown Copyrights, 1975

Case History Number 91: Sustained High Inspired P_{O_2} Without Toxic Sequelae

PHILIP S. GIBBS, MD*
S. S. MOORTHY, MD†
ALVIN M. LoSASSO, MD‡
Indianapolis, Indiana§

PULMONARY disorders such as infection, atelectasis, barotrauma, and pulmonary O_2 toxicity may occur during treatment of patients with respiratory failure. The development of O_2 toxicity, a well-documented hazard,[1] depends on the duration and dosage of O_2 administration[2] and a high P_{IO_2}.[3] However, when O_2 is needed, it must be given.

We describe a case of a child with respiratory failure who was exposed to high inspired partial pressures of O_2 for nearly 3 weeks without developing overt O_2 toxicity.

CASE REPORT

A 2-year-old girl was admitted with acute respiratory failure after aspirating a liquid hydrocarbon (paint thinner). Soon after the aspiration, the patient was given first aid at her home and transported to the hospital with mouth-to-mouth resuscitation. She was oxygenated and intubated upon arrival in the emergency room.

The admittance examination revealed an obtunded, cyanotic, well-developed child in respiratory distress. Her rectal temperature was 37.8° C, pulse rate was 160/min, and respiratory rate was 60/minute. Ascultation of the lungs revealed bilateral coarse rales. Other systems were normal. A chest x-ray at this time demonstrated bilateral alveolar infiltrates (fig 1).

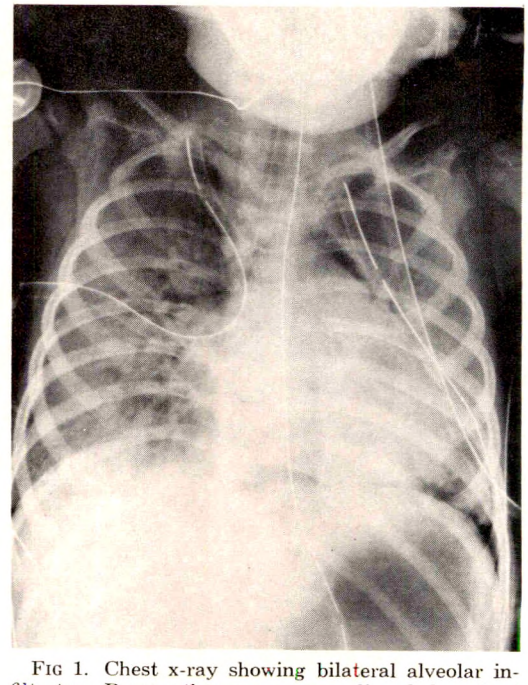


FIG 1. Chest x-ray showing bilateral alveolar infiltrates. Pneumothoraces were relieved by chest tubes.

The patient had a convulsive episode, during which she was accidentally extubated. She was subsequently maintained on 80 to 90% inspired O_2 for 2 days by mask, when she showed further deterioration. She was

*Assistant Professor.
†Assistant Professor.
‡Associate Professor.
§Department of Anesthesiology, Indiana University School of Medicine, Indianapolis, Indiana 46202.

This feature was conducted by Robert K. Stoelting, MD, Associate Editor, Professor, Department of Anesthesiology, Indiana University School of Medicine, Indianapolis, Indiana 46202.

is followed by proliferation of cuboidal granular pneumatocytes (type II) to regenerate the epithelial lining.[2] As a result of these studies, the hypothesis that factors supplied by the blood are necessary for O_2 to become toxic has been proposed.[3] The mechanisms involved in this complex process remain to be identified conclusively.

Several human experiments have confirmed that 50% O_2 can be inhaled by normal subjects for extended periods without clinical evidence of pulmonary irritation.[4,5] There is increasing evidence that critically ill patients cannot be compared with normal subjects to predict the development of pulmonary O_2 injuries, but no conclusive evidence is currently available that those with preexisting pulmonary disease are *more* sensitive to the toxic effects than are normal volunteers.[6] Although some investigators feel that wide alveolar-arterial O_2 tension differences, as observed in this paper, somehow protect against pulmonary O_2 damage,[7] this observation has not been substantiated in animals given normobaric O_2 levels.[8]

The treatment of significant hypoxemia, as indicated by the authors, is essential and should supersede but not eliminate our concerns about the effects of hyperoxia. Prolonged respiratory insufficiency is a situation where O_2 toxicity becomes an increasing problem. Technics aimed at reducing the shunt fraction, such as carefully selected and monitored ventilatory patterns and the addition of positive end-expiratory pressure (PEEP), may reduce significantly the ambient O_2 requirement and/or the duration of exposure. In conditions where there is evidence of air-block, PEEP must be used with caution, since it can aggravate emphysematous changes and increase CO_2 retention.

The possible predisposing effect of intermittent positive-pressure ventilation (IPPV) on pulmonary O_2 toxicity remains controversial. Animal studies suggest that mechanical overventilation leads to a loss of pulmonary surfactant, with augmentation of terminal atelectasis, but IPPV with normal tidal volumes does not impair pulmonary function.[9] Such studies, if applicable to the human, reinforce the need for precision in ventilator care.

The remark in the present report that "there is no radiographic evidence of permanent damage to the lungs" should not be misinterpreted to indicate that no impairment exists. Major abnormalities in vital capacity and other measures of pulmonary function may be present for weeks despite a "normal" Pao_2 and chest film.[10] If these patients have another pulmonary insult, such as pneumonia or bronchitis, before full recovery, they experience what seems to those unaware of the persistent underlying disease to be a disproportionate increase in O_2 and pulmonary-support requirements.

This clinical report corroborates the contention that maintaining Pao_2 at levels which provide for the aerobic metabolism of vital organs does not invariably result in serious pulmonary O_2 damage, even though high inspired O_2 concentrations are required. This may reflect the effects of some as yet poorly understood protective factors. In any event early recognition and rapid correction of complications, meticulous ventilator management, and appropriate respiratory physiotherapy are mandatory in order to achieve such a successful outcome.

REFERENCES

1. Lavoisier: Quotes from Schmiedhausen RG: Inaugural dissertation. Halle, 1909

2. Weibel ER: Oxygen effect on lung cells. Arch Intern Med 128:54-56, 1971

3. Kistler GS, Caldwell PRB, Weibel ER: Development of fine structural damage to alveolar and capillary lining cells in oxygen-poisoned rat lungs. J Cell Biol 32:605-628, 1967

4. Barach AL, McAlpin R: Negative results of oxygen therapy in polycythemia vera. Am J Med Sci 185:178-181, 1933

5. Clark JM, Lambertsen CJ: Pulmonary oxygen toxicity: a review. Pharmacol Rev 23:37-133 (table 3), 1971

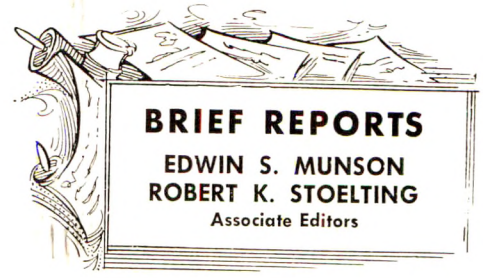
6. Winter PM, Smith G: The toxicity of oxygen. Anesthesiology 37:210-241, 1972

7. Winter PM, Gupta RK, Michalski AH, et al: Modification of hyperbaric oxygen toxicity by experimental venous admixture. J Appl Physiol 23: 954-963, 1967

8. Miller VM, Waldhausen JA, Rashkind WJ: Comparison of oxygen poisoning of the lung in cyanotic and acyanotic dogs. N Engl J Med 282: 943-947, 1970

9. Lee CJ, Lyons JH, Konisberg S, et al: Effects of spontaneous and positive-pressure breathing of ambient air and pure oxygen at one atmosphere pressure on pulmonary surface characteristics. J Thorac Cardiovasc Surg 53:759-769, 1967

10. Caldwell PRB, Lee WL Jr, Schildkraut HS, et al: Changes in lung volume diffusing capacity and blood gases in men breathing oxygen. J Appl Physiol 21:1477-1483, 1966



Prevention of Hypothermia During Cystoscopy in Neonates

MICHAEL B. MEYERS, MD*
TAE H. OH, MD†
New Haven, Connecticut‡

PROBLEMS of intraoperative temperature control in the neonate are well documented. Use of warming blankets, overhead warming lights, humidified warm gases, heated IV fluids, and warm fluid-filled gloves have facilitated better temperature control. However, such modalities are not always adequate.[1] The following report presents an additional method of temperature control during neonate cystoscopy, during which irrigation of the bladder may result in hazardous hypothermia.

REPORT OF A CASE

A 10-week-old, 2.8 kg Caucasian infant was admitted with anemia and *E. coli* sepsis secondary to obstructive uropathy. As diagnostic workup revealed posterior urethral valves, he was scheduled for cystoscopy and fulguration. Preoperatively, the patient was given 0.1 mg of atropine IV and brought to the cystoscopy suite. Following an uneventful awake tracheal intubation, halothane, N_2O, and O_2 were administered with a nonrebreathing system. Despite the use of a warming blanket, overhead warming lights, and warm humidified gases, tympanic membrane temperature showed a precipitous fall at the beginning of cystoscopy, using continuous bladder irrigation with sterile, 23.5° C, water. At a temperature of below 35° C, the procedure was abandoned and he was returned to the recovery room, with a temperature of 34.5° C.

Seven days later, the infant was again taken to the cystoscopy suite for cystoscopy and perineal urethroplasty. After awake tracheal intubation, anesthesia was induced with halothane-N_2O-O_2 via a nonrebreathing system. Temperature was controlled with radiant heat lights and a warming blanket and mattress, but the lithotomy position made possible only minimal contact

*Resident of Anesthesiology.
†Assistant Professor of Anesthesiology.
‡Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut 06510.
Reprint requests to Dr. Oh.
Paper received: 12/1/75
Accepted for publication: 1/23/76

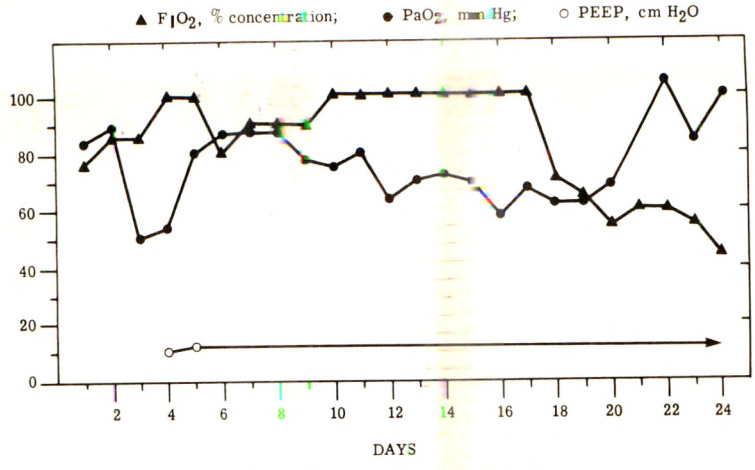


FIG 2. Course of ventilation and O_2 exchange.

reintubated and put on CPAP with 10 cm H_2O pressure and then on controlled ventilation on the Engström ventilator with PEEP. Subsequently, the ventilator was changed to a MA-I to provide an assist-control mode of ventilation.

The patient developed a right pneumothorax on the 4th day after admission and on the left side on the 5th day, both of which were treated by insertion of chest tubes with underwater seal and negative pressure suction. A tracheostomy was performed on the 8th day because of no improvement in her clinical status. She continued to require mechanical ventilatory assistance with high levels of inspired O_2.

Very high peak inspiratory pressures, approaching 100 cm H_2O were necessary to achieve adequate ventilation. To achieve these pressures, we had to change the type of volume ventilator from the MA-I to the Engström, and finally to the Emerson due to the mechanical limitations of the two former ventilators.

The patient began to show improvement in oxygenation from the 20th day after admission, at which time she required an F_{IO_2} of 0.55 to give a Pa_{O_2} of 76 torr (fig 2). Later, her course was one of progressive improvement. She was finally weaned from ventilatory assistance and supplemental O_2, and was discharged from the hospital 50 days after admission.

DISCUSSION

This case illustrates both the difficulties in the management of a child with respiratory failure and an absence of significant reversible manifestations of O_2 toxicity [illegible] high inspired P_{IO_2}, needed to maintain an acceptable Pa_{O_2}, although the high ventilatory pressures required produced barotrauma.

In our patient, radiologic delineation of pulmonary O_2 toxicity was difficult because of the underlying primary disease process. If there were changes, these did not persist when the patient improved. It has been reported that some patients in respiratory failure are more resistant to pulmonary O_2 toxicity than normal volunteers.

Prolonged exposure to high P_{IO_2} of both adult and pediatric patients with respiratory failure without developing toxicity, has

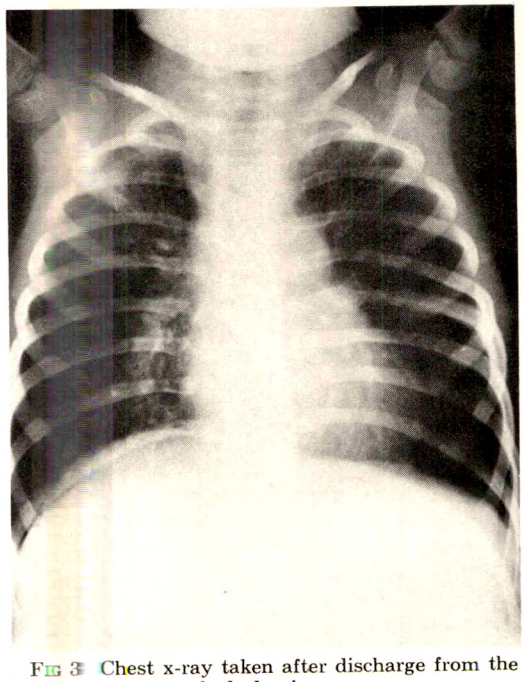


FIG 3. Chest x-ray taken after discharge from the hospital shows marked clearing.

been reported.[4] Why some individuals develop such toxicity while others do not is difficult to explain. High levels of such enzymes as superoxide dismutase may give protection.

Patients with respiratory failure should be closely monitored, and all effective methods should be used to reduce P_{IO_2} while maintaining an optimal P_{aO_2}.[5] However, a calculated risk must sometimes, as in our case, be taken. After subsequent complete clearance of the disease process, there was no noticeable radiologic evidence of permanent damage to the lungs (fig 3).

REFERENCES

1. Barbar RE, Lee J, Hamilton WK: Oxygen toxicity in man. A prospective study in patients with irreversible brain damage. N 283:1478-1484, 1970

2. Fairley HB: Management of respiratory failure. Regional Refresher Course in Anesthesiology. Edited by SG Hershey. American Society of Anesthesiologists, 1973, vol 1, pp 41-55

3. Wolfe WG, DeVries WC: Oxygen toxicity. Annu Rev Med 26:203-217, 1975

4. Winter PM: Pulmonary oxygen toxicity, Refresher Course in Anesthesiology. Edited by SG Hershey. American Society of Anesthesiologists, 1974, vol 2, pp 163-178

5. Bendixen HH, Egbert LD, Hedley-Whyte J, et al: Respiratory Care. St. Louis, The CV Mosby Company, 1965

6. Nash G, Blennerhassett JB, Pontoppidan H: Pulmonary lesions associated with oxygen therapy and artificial ventilation. N Engl J Med 276:368-373, 1967

Comment

ROBERT K. STOELTING, MD

Pulmonary O_2 toxicity is a function of the inspired O_2 partial pressure and the duration of administration. The use of PEEP may permit the physician to achieve acceptable arterial oxygenation with inspired O_2 concentrations unlikely to introduce the hazard of pulmonary O_2 toxicity. Nevertheless, occasional patients, like the one described in this report, still require high O_2 partial pressures to prevent the permanent organ damage resulting from arterial hypoxemia.

It is fortunate that pulmonary O_2 toxicity does not always occur, as the physician has no choice but to use whatever O_2 dose is necessary. Indeed, the critically ill patient may respond differently than the normal volunteer. For example, patients with large right-to-left intrapulmonary shunts survive high O_2 concentrations for over a month.[1] Thus, reduced arterial oxygenation may in some way protect against adverse pulmonary effects of the high inspired O_2 concentrations used to treat the hypoxemia.

REFERENCE

1. Hedley-Whyte J: Control of the uptake of oxygen. N Engl J Med 279:1152-1158, 1968

Discussion

EDWIN L. GRESHAM, MD
Associate Professor of Pediatrics and
Obstetrics and Gynecology
Section of Fetal-Neonatal Medicine
Department of Pediatrics
Indiana University School of Medicine
Indianapolis, Indiana

This paper describes one example of the complex pulmonary problems encountered with increasing frequency by specialists in pulmonary disease. It alludes to the ever-present dilemma of the pulmonologist, who must decide how much supplemental O_2 is required and what other mechanical and/or surgical methods are necessary to prevent the devastating effects of hypoxemia, while avoiding complicating barotrauma and O_2 poisoning.

Shortly after the discovery of O_2 in the atmosphere, Lavoisier[1] found that the pure gas produced inflammatory reactions in the lungs. Since those early studies, many investigators have added to our knowledge, but even now the mechanism(s) by which O_2 damages tissue and the nature of cellular resistance to its toxic action are not completely understood.

Observations in animals have indicated that high inspired O_2 concentrations lead to primary destruction of alveolar capillary endothelial cells. Squamous epithelial c (type I) are damaged secondarily, ar

with the warming mattress. Tympanic temperature, which was 38° C during the induction of anesthesia, once again began to fall at the beginning of continuous bladder irrigation. After 30 minutes, the temperature had decreased to 35° C. At this point, a standard blood-warming coil was interposed between the bladder irrigation system and the cystoscope and immersed in a water bath maintained at 40° C. The cystoscopy with urethroplasty continued for an additional 20 minutes. Anesthesia was completed without incidence, and in the recovery room, the infant's temperature was 35.8° C.

DISCUSSION

The critical temperature of the newborn undergoing cystoscopy in the lithotomy position is often compromised by the use of a relatively cool solution (at room temperature) for the continuous irrigation of a core compartment. The body mass of the neonate is approximately 5% that of the adult, while body surface area is only 15%. Therefore, there is a threefold greater capacity for heat dissipation. The neonate also lacks the subcutaneous fat and tissue of the adult, which normally provide insulation against heat loss.[2] Core conductance to the periphery also is greater in the neonate, facilitating greater heat loss over a shorter period of time.[3,4]

Most anesthetic agents contribute to hypothermia by reducing afferent stimuli, preventing shivering and muscular activity, inhibiting metabolism, and causing cutaneous vasodilation. Inadvertent hypothermia is one cause of neonatal morbidity and mortality.[5] Continuous irrigation of a highly vascular core compartment with a warm aqueous solution may facilitate maintenance of a normal body temperature when used from the start of neonate cystoscopy.

REFERENCES

1. Shim WKT, Halford P: Method for maintaining the neonate's intraoperative core temperature. Surgery 75:416-420, 1974

2. Mo il KJ, Blackburn MG: Temperature regulation in the neonate: a survey of pathophysiology of thermal dynamics and of the principles of environmental control. Clin Pediatr 12:634-639, 1973

3. Br k K: Temperature regulation in the newborn infant. Biol Neonate 3:65-119, 1961

4. Adamsons K Jr, Towell ME: Thermal homeostasis in the fetus and newborn. Anesthesiology 26: 531-548, 1965

5. Dilworth NM: The importance of changes in body temperature in paediatric surgery and anaesthesia. Anaesth Intensive Care 1:480-485, 1973

Estimation of Anesthetic Solubility in Blood

ALFRED FEINGOLD, MS MD*

PHARMACOKINETICS of inhalation anesthetics classically describe the blood/gas partition coefficient (B/G) as an important determinant of the speed of induction of and emergence from inhalation anesthesia. For this reason, the solubility in blood has been determined for virtually all anesthetics.

This blood solubility may be divided into 3 major components: solubility in lipids, water, and plasma proteins.[1-4] Featherstone's group[1] and Lowe† have reasoned that B/G may be estimated by addition of 0.8 times the water/gas partition coefficient (W/G) and 0.005 times the fat/gas partition coefficient (F/G). These coefficients correspond to the water and lipid content of normal blood and result in the equation:

$$B/G = 0.8\ W/G + 0.005\ F/G \qquad (I)$$

The application of this formula, however,

†Dose-regulated Penthrane® Anesthesia, Abbott Laboratories, North Chicago, Illinois.

*Assistant Professor, Department of Anesthesiology, University of Miami School of Medicine, and Veterans Administration Hospital, Miami, Florida 33152.

This study was supported in part by NIH Grant #GM 16498 and funds from the Miami Veterans Administration Hospital.

Paper received: 9/2/75

Accepted for publication: 1/22/76

TABLE

Reported and Calculated Partition Coefficients for 13 Anesthetics

Agent	Reported*			Calculated†	Percent difference‡ (percent)
	Water/gas	Fat/gas	Blood/gas	Blood/gas	
Diethyl ether	13.0	50 (66)	12.0	12.04 (12.23)	0 (−2)
Trichloroethylene	1.7 (1.51)	600 (740)	9.0	8.70 (8.74)	+3 (+3)
Halothane	0.80	155 (185)	2.4	2.56 (2.56)	−7 (−7)
Isoflurane	0.62 (0.70)	68 (94.5)	1.4	1.36 (1.56)	+3 (−11)
Nitrous oxide	0.47	1.4	0.47	0.43 (0.43)	+8 (+8)
Methoxyflurane	4.5 (3.5)	670 (890)	11.0	12.00 (12.02)	−9 (−9)
Fluroxene	0.85	34 (43.8)	1.4	1.16 (1.20)	+17 (+15)
Chloroform	4.0	280	8.0	6.88 (6.36)	+14 (+21)
Enflurane	0.78	70	1.9	1.53 (1.39)	+19 (+27)
Divinyl ether	1.4	40 (59)	2.6 (2.2)	1.71 (1.84)	+34 (+16)
Xenon	0.085 (0.097)	1.3	0.14	0.09 (0.10)	+35 (+29)
Ethylene	0.09	0.95	0.15	0.09 (0.09)	+40 (+40)
Cyclopropane	0.21	8 (14)	0.55	0.28 (0.33)	+49 (+40)

*From Steward.[5] ( ) values from Lowe when they differ more than ±10% from those reported by Steward.

†B/G = 0.88 W/G + 0.012 F/G (for Steward's data). ( ) B/G = 0.89 W/G + 0.01 F/G (for Lowe's data).

‡Percent difference = $100\left(1 - \frac{\text{calculated B/G}}{\text{reported B/G}}\right)$.

fails to explain large amounts of blood solubility, attributed to protein solubility or to protein binding.

It seemed worthwhile to examine a large number of anesthetic agents and to determine by numerical analysis the best coefficients of equation I. In addition to producing a simple formula for approximating B/G, this might further identify those inhalation anesthetics whose blood solubility is strongly influenced by plasma proteins.

METHODS

Using the summarized data of Lowe and of Steward and associates[5] for B/G, W/G, and F/G in man (at 37° C), 13 anesthetics were studied. Since the values recommended by these authors differ, an arbitrary tolerance of ±10% was chosen. When Steward's values were within ±10% of those from Lowe, Steward's values were used; when Lowe's values were outside this range, they were treated separately and appear separately in the table.

These data resulted in an overconditioned matrix of 13 equations with 2 unknown coefficients, x and y:

$$B/G = x\ W/G + y\ F/G \qquad (II)$$

A digital computer program minimized the root-mean-square difference between B/G calculated from equation II and those values reported. A separate estimate of x and y was obtained for the data which included Lowe's values. For both estimates of x and y, the percent difference between the reported and the calculated B/G was determined.

RESULTS

The best coefficients for the 13 anesthetics studied are x equals 0.88 and 0.89 and y equals 0.012 and 0.01 for Steward's and Lowe's data, respectively. The table lists the anesthetics in order of the mean absolute percent difference. The mean percent differences for diethyl ether, trichloroethylene, halothane, isoflurane, nitrous oxide, and methoxyflurane are within the ±10% tolerance selected for this study. Enflurane, cyclopropane, fluroxene, divinyl ether, chloroform, ethylene, and xenon all have more anesthetic dissolved in blood than can be accounted for by this simple equation. The greatest discrepancy between the calculated and reported B/G occurs for cyclopropane (+40 to +49%), ethylene (+40%), xenon (+29 to +35%), divinyl ether (+16 to +34%), and enflurane (+19 to +27%).

DISCUSSION

The accuracy of any equation for predicting B/G from W/G and F/G depends in

part on the accuracy of the values used. For this reason, 2 sources of summarized partition coefficients were used. The 2 sets of W/Gs and B/Gs differ in an unsystematic way. However, the F/Gs from Lowe are consistently higher than those from Steward, reflecting different methodologies.

The order of the anesthetics in the table is little affected by choosing the values of 1 author rather than the other. The coefficients calculated for both sets of partition coefficients are sufficiently close to suggest the following equation as the best estimate of B/G:

$$B/G + 0.89\ W/G + 0.011\ F/G \quad (III)$$

Several inhalation anesthetics have been shown to bind to proteins. Featherstone[1] showed that 53% of the cyclopropane dissolved in whole blood resulted from protein binding. Schoenborn demonstrated the binding of xenon to hemoglobin[6] and cyclopropane to myoglobin.[7] Cowles and colleagues[8] reported that the B/G of cyclopropane and ethylene increase at low concentrations, which is consistent with protein binding.

Normal blood is reported to contain 81% water and 0.6% lipid.[9] These values are slightly larger than those used in previous estimates; however, the estimation of B/G within ±10% for 6 of the anesthetics requires coefficients which represent even greater water and lipid content. This suggests that all of these 6 anesthetics have significant solubility in plasma proteins, as shown for halothane by Lassberg and Hedley-Whyte.[2]

Even with these larger coefficients, there remains a large discrepancy between the calculated and reported B/G for 7 anesthetics. Four of these (fluroxene, chloroform, enflurane, and divinyl ether) have not been previously reported to have significant solubility in plasma proteins or to undergo significant protein binding.

REFERENCES

1. Featherstone RN, Muehlbaecher C, DeBon FL, et al: Interactions of inert anesthetic gases with proteins. Anesthesiology 22:977-981, 1961

2. Lassberg LH, Hedley-Whyte J: Halothane solubility in blood and solutions of plasma proteins. Anesthesiology 32:351-356, 1970

3. Lowe HJ: Determination of volatile organic anesthetics in gases, blood and tissues, Gas Chromatography. Edited by SR Bender, HS Knoman. New York, Grune and Stratton Company, 1968, pp 194-209

4. Lowe HJ, Hagler K: Determination of volatile organic anaesthetics in blood, gases, tissues and lipids: partition coefficients, Ciba Foundation Symposium on Gas Chromatography and Biology in Medicine. Edited by R Porter. London, J & A Churchill, Ltd, 1969, pp 86-103

5. Steward A, Allott PR, Cowles AL, et al: Solubility coefficients for inhaled anaesthetics for water, oil and biological media. Br J Anaesth 45: 282-293, 1973

6. Schoenborn BP: Binding of xenon to horse haemoglobin. Nature 208:760-762, 1965

7. Schoenborn BP: Binding of cyclopropane to sperm whale myoglobin. Nature 214:1120-1122, 1967

8. Cowles AL, Borgstedt HH, Gillies AJ: Solubilities of ethylene, cyclopropane, halothane and diethyl ether in human and dog blood at low concentrations. Anesthesiology 35:203-211, 1971

9. Biological Handbooks: Blood and Other Body Fluids. Edited by DS Dittmer. Federation of American Societies for Experimental Biology, 1961, pp 12, 19, 79

Significance of Pco_2 Within Low-Pressure Endotracheal Tube Cuffs

PAUL R. LEVESQUE, MD*

STANLEY and coworkers[1,2] recently demonstrated that the pressure within air-filled endotracheal tube cuffs increases during N_2O inhalation. Since this phenomenon is the result of transfer of N_2O into the cuff gas space, it is also likely that the CO_2

*Associate Professor of Anesthesia, Tufts University School of Medicine; Anesthesiologist, New England Medical Center Hospital, Boston, Massachusetts 02111.

Paper received: 7/8/75

Accepted for publication: 12/8/75

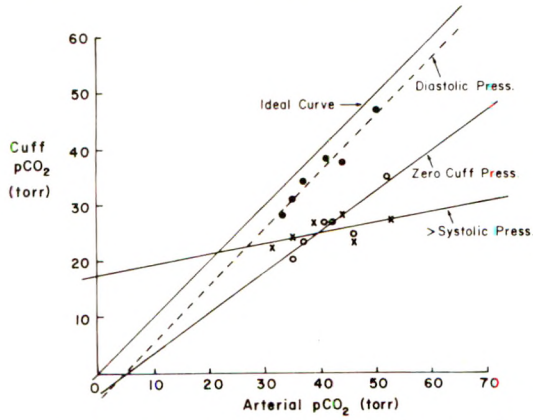


FIGURE. Regression lines illustrating the close correlation between cuff Pco_2 when cuff pressure approximates arterial diastolic pressure (dotted line).

partial pressure within the cuff might reflect the $Paco_2$ of the tracheal mucosa.

METHODS

Measurements were made on 6 anesthetized, intubated adult patients (following informed consent) undergoing surgical procedures lasting 4 hours or more. A radial artery cannula was inserted preoperatively for blood pressure monitoring and arterial blood sampling. Anesthesia was maintained by 40 to 60% N_2O with O_2 and enflurane.

Following induction of anesthesia, an NCC 8 mm ID polyvinyl endotracheal tube, equipped with a thin-wall, high-residual-volume, low-pressure flabby cuff, was inserted and inflated with sufficient air (12 to 15 ml) to raise the cuff pressure 10 to 20 torr above arterial systolic pressure (120 to 200 torr). Intracuff pressure was monitored by an aneroid manometer connected to the pilot tube. Forty-five minutes later, arterial blood and cuff gas were sampled. To avoid contamination of the gas sample by air from the pilot tube, the first 2 ml portion was discarded and a 3-ml sample taken for Pco_2 measurement.

Cuff pressure was then adjusted to equal arterial diastolic pressure (60 to 80 torr), and 45 minutes later the same sampling procedure was carried out. Finally, cuff pressure was lowered to zero but tracheal seal preserved by residual air remaining in the flabby cuff. Sampling was done 45 minutes later, as above, and results were analyzed electronically.

RESULTS AND COMMENTS

Close correlation is demonstrated (figure) between cuff Pco_2 and $Paco_2$ when the intracuff pressure approximates patient's diastolic pressure: regression equation is $Y = 1.03x - 5.28$ and $r = 0.9076$. These results show that diffusion from the tracheal mucosa through cuff membrane occurs. Indeed, when intracuff pressure is allowed to exceed arterial systolic pressure, no correlation exists between cuff Pco_2 and $Paco_2$: regression equation is $Y = 0.187x + 17.614$ and $r + 0.619$. When cuff pressure is zero but tracheal seal is preserved, the regression equation is $Y = 0.715x - 3.819$ with $r = 0.897$. This indicates either that equilibrium was taking place between cuff Pco_2 and mean airway $Paco_2$, or that the surface area of contact of the cuff with tracheal mucosa was too small to achieve rapid equilibrium with $Paco_2$. (Airway tension was not measured.)

Clinical Applications.—1. When tracheal seal cannot be achieved with low cuff pressure (20 torr), at least cuff pressure should not exceed the patient's arterial diastolic pressure. This should prevent impairment of mucosal blood supply and avoid tracheal damage.

2. Whenever arterial cannulation is contraindicated (for instance, in patients with hemophilia, peripheral vasculitis, etc) a close approximation of $Paco_2$ can be achieved by sampling gas from the endotracheal tube cuff after 1 hour of cuff inflation at approximately patient diastolic pressure. Whether cuff Pco_2 equilibrates with arterial or venous Pco_2 is unknown, but (arterialized) venous Pco_2 has been demonstrated to approach $Paco_2$ during anesthesia.[3]

REFERENCES

1. Stanley TH, Kawasimura R, Graves C: Effects of nitrous oxide on volume and pressure of endotracheal tube cuff. Anesthesiology 41:256-262, 1974

2. Stanley TH: Nitrous oxide pressures and volumes of high and low-pressure endotracheal tube cuffs in intubated patients. Anesthesiology 42:637-640, 1975

3. France CJ, Eger EI II, Bendixen HH: The use of peripheral venous blood for pH and carbon dioxide tension determinations during general anesthesia. Anesthesiology 40:311-314, 1974

Shearing Hazard of Intra-Arterial Teflon Catheters

EDWARD A. TALMAGE, MD*

Sayre, Pennsylvania †

Downs and associates,[1] evaluating several "needle-through-catheter" intravascular devices for percutaneous radial artery cannulation, found the 20-gauge Longdwel® Teflon catheter‡ to be accompanied by significantly fewer vascular complications than the 18-gauge Longdwel or the 18 or 20-gauge Argyle Medicut®.§ The 20-gauge is also recommended by others[2] for dorsalis pedis artery cannulation.

In evaluating the 20-gauge Vicra Quik-Cath®‖ Teflon needle-catheter combination, we often detected a grating sensation as the needle and catheter were advanced into the artery. Examination upon withdrawal revealed a frayed and crimped catheter tip, with distorted, irregular edges and sharp, tentacle-like projections (figure). It was first thought that calcified vessel walls might be producing this effect, but the grating sensation could be detected immediately after passage through the skin before the vessel wall was contacted, and the same deformity was produced after a single passage through the skin. Advancement of such "sheared" or frayed catheters into the artery after puncture of the vessel was either difficult, accompanied by the grating sensation, or impossible, due to resistance to catheter entry into the vessel. The inner cannula tip might be in the vessel lumen, with a pulsating blood return, yet catheter advancement would be impeded through impingement of its distorted edges on the vessel wall. As passage of such rough-edged catheters partly or completely into the vessel increases the incidence of hematoma formation, the grating sensation is a clear indication to withdraw and discard such cannulas, to avoid any possible damage to the intima and media of the vessel wall. The grating sensation, possibly accompanied by resistance to the entrance of the catheter into the vessel, is best appreciated when the operator grasps the cannula directly in his fingers, as use of a syringe or a Longdwel outer guard as a handle may dampen the sensation so much that it escapes detection.

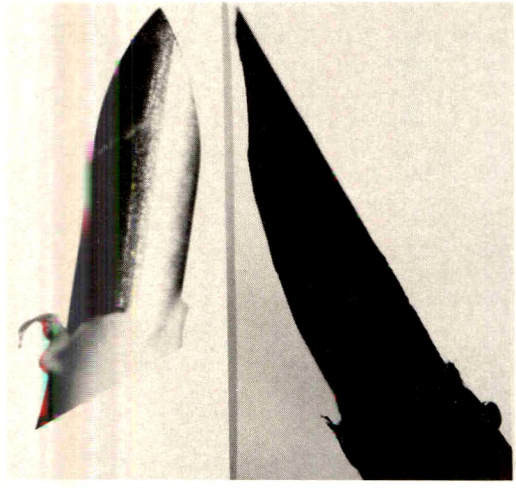


FIGURE. Enlarged view of representative catheter and cannula showing sharp edges and projections (approx. x 25).

The tip of the 20-gauge Longdwel catheter has revealed similar structural alterations and deformities of its leading edge. Some catheters, regardless of brand, appear more subject to shearing than others. Inner cannulas just larger than optimum may cause excessive stretching of the catheter edge, rendering it more subject to shearing upon passage through skin and/or vessel wall.

One of the goals in the development of

‡Becton-Dickinson Company, Rutherford, New Jersey.

§Sherwood Industries, St. Louis, Missouri.

‖Travenol Laboratories, Deerfield, Illinois.

*Clinical Associate Professor of Anesthesiology, Hahneman Medical College.

†Department of Anesthesiology, Guthrie Clinic-Robert Packer Hospital, Sayre, Pennsylvania 18840.

Paper received: 10/6/75

Accepted for publication: 11/19/75

these catheters has been to make the junction between the needle and the catheter as smooth as possible, to facilitate passage through the skin, entrance into the vessel, and slipping the catheter off the needle into the vessel once the vessel wall has been punctured and a good flow obtained. This has generally been accomplished by tapering the distal tip of the catheter, reducing the outside diameter to the minimum compatible with structural integrity of the catheter, in most cases a knife edge. Theoretically, such a knife-edged taper might be easily crimped or roughened if the catheter material were not sufficiently strong to resist the shearing forces to which the edge is subjected in its passage through the skin, subcutaneous tissues, and vessel wall.

Perhaps the knife edge on the catheter tip could be modified to a somewhat rounded tip of just sufficient radius to resist the above-described shearing forces, care being taken to avoid oversize inner cannulas. Such rounded tips should present little or no impediment to passage through normally elastic skin or vessel walls. Alternatively, one could pre-puncture the skin with a slightly larger needle, but the vessel wall might still distort the catheter edge. It would seem prudent to avoid intra-arterial or intravenous advancement of catheters whose passage has been accompanied by the grating sensation described.

ACKNOWLEDGMENT

The microphotographs were made by Drs. Donald Weaver and John Kelly, Department of Pathology, Guthrie Clinic-Robert Packer Hospital.

REFERENCES

1. Downs JB, Rackstein AD, Klein EF Jr: Hazards of radial-artery catheterization. Anesthesiology 38:283-286, 1973

2. Johnstone RE, Greenhow DE: Catheterization of dorsalis pedis artery. Anesthesiology 39:654-655, 1973

Evaluation of Larynx and Trachea by Xeroradiography

S. S. MOORTHY, MB, BS, MD*
ALVIN M. LoSASSO, MD†
HAROLD KING, MD‡
EDMUND FRANKEN, MD§
Indianapolis, Indiana‖

PATHOLOGIC changes in the larynx and the trachea may result from tracheal intubation.[1] Xeroradiography, which involves exposing a highly charged selenium plate to x-rays,[2,3] gives excellent images of the larynx and trachea for evaluation both before and after intubation.

In xeroradiography, the surface of the plate becomes conductive to the exposed areas and acquires a charged image depicting radiation intensities. This plate is exposed to a cloud of blue powder which is attracted to the plate according to the intensity of charge. The final image can be

*Assistant Professor, Department of Anesthesiology.
†Associate Professor, Department of Anesthesiology.
‡Professor, Department of Surgery; Director, Section of Thoracic and Cardiovascular Surgery.
§Professor, Department of Radiology.
‖Indiana University School of Medicine, Indianapolis, Indiana 46202.
Paper received: 1/5/76
Accepted for publication: 2/13/76

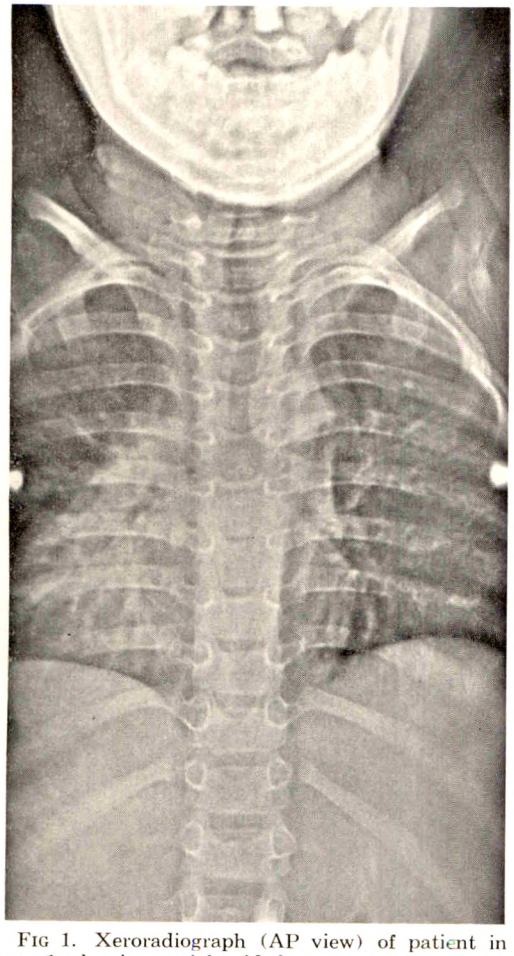


FIG 1. Xeroradiograph (AP view) of patient in case 1, showing a right-sided aorta pressing on the trachea. (The image is reversed.)

viewed directly or transferred to a plastic-coverec paper. When printed, the sides of the image are reversed.

We report 2 cases and a prospective study, to aler the anesthesiologist to the use of xeroradiography as a noninvasive approach to detect abnormalities of the larynx and trachea and for evaluation of the airway after intubation.

CASE REPORTS

Case 1. Detection of changes in the trachea before operation.—A 3-year-old boy was admitted for repair of tetralogy of Fallot. He was in no preoperative respiratory distress. However, preoperative xeroradiography revealed a right-sided aortic arch pressing on the trachea (fig 1), alerting the physicians to the danger of postoperative airway obstruction from tracheal compression. This patient had an uneventful postoperative course.

Case 2. Subglottic stenosis and web following prolonged intubation.—A 10-year-old girl was admitted for repair of cardiac defects and takedown of pulmonary artery banding under cardiopulmonary bypass. Postoperatively, the patient required mechanical ventilatory support for 7 days by indwelling uncuffed endotracheal tube. Following tracheal extubation on the 7th day, only hoarseness was present. She was discharged on the 17th postoperative day. On the 25th postoperative day, she was readmitted with acute upper-airway obstruction.

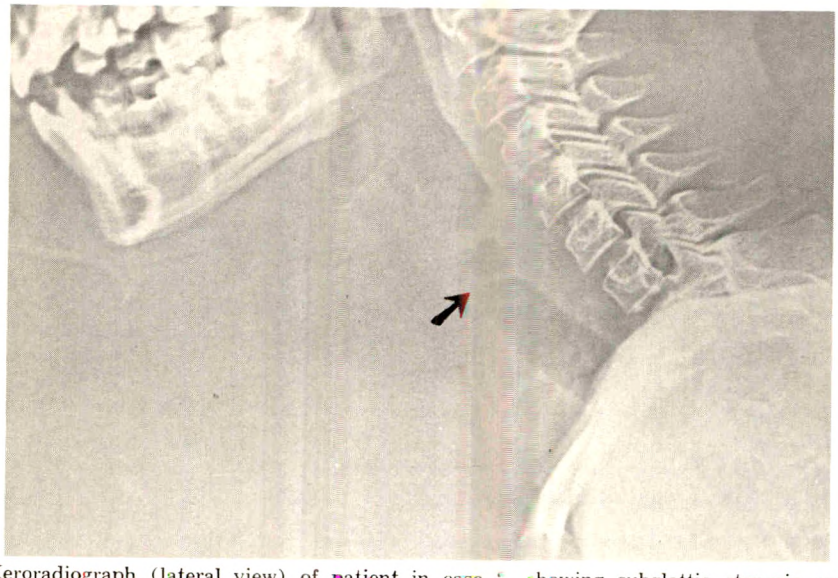


FIG 2. Xeroradiograph (lateral view) of patient in case 2, showing subglottic stenosis and (arrow) laryngeal web.

Xeroradiography of the larynx and trachea showed subglottic stenosis and a laryngeal web (fig 2). The patient underwent tracheostomy followed by repeated tracheal dilations.

PROSPECTIVE STUDY

To determine the incidence of laryngotracheal abnormalities as revealed by xeroradiography, we studied 16 pediatric patients (4 to 14 years) scheduled for elective open-heart operations. All were endotracheally intubated with polyvinyl-chloride tubes whose size (French) was determined by the formula "age + 17," modified as indicated by clinical judgment. In only 1 patient was a cuffed tube used. Fourteen of the patients were intubated for 28 hours, one for 8 hours, and one for 72 hours.

Of the 16 patients, 14 showed no laryngeal or tracheal changes on xeroradiography at 24 to 72 hours after extubation. Narrowing of the trachea by 1 mm was seen in 2 patients after intubation (uncuffed) for 28 and 72 hours, respectively.

DISCUSSION

While only minimal changes were observed by xeroradiography in 2/14 patients studied, more prolonged intubation, use of low-volume, high-pressure cuffs, or xeroradiography several days after extubation might have shown different results. Indeed, the 1 patient who developed a laryngeal web after 7 days of intubation did not manifest symptoms until several days postextubation. Perhaps xeroradiography during the asymptomatic period would have revealed this lesion to be forming. The boy examined by xeroradiography before intubation, who then showed tracheal compression, was asymptomatic.

ACKNOWLEDGMENT

The authors thank Dr. Eugene Klatte, Professor and Chairman, and Dr. Huen Yune, Department of Radiology, for their help, and Miss Linda Hicks for secretarial assistance. The authors thank Dr. Robert K. Stoelting for his helpful suggestions.

REFERENCES

1. Symchych PS, Cadotte MD: Squamous metaplasia and necrosis of the trachea complicating prolonged nasotracheal intubation of small newborn infants. J Pediatr 71:534-541, 1967

2. Holinger PH, Lutterbeck EF, Bulger R: Xeroradiography of the larynx. Ann Otol 81:806-808, 1972

3. Doust BD, Ting YM: Xeroradiography of larynx. Radiology 110:727-730, 1974

Pneumatocele of the Larynx: A Complication of Percutaneous Transtracheal Ventilation

EDWARD CARDEN, MA, MB, BChir, FRCP(C)*
THOMAS C. CALCATERRA, MD†
ALLEN LECHTMAN, MD‡
Los Angeles, California§

REPORT OF A CASE

A 27-YEAR-OLD Hawaiian suffered neck trauma in an automobile accident, requiring emergency tracheostomy through the 2nd and 3rd tracheal rings. His larynx was explored, and extensive damage to the right thyroid lamina and right vocal cord was repaired by mucosal approximation and

*Associate Professor, Department of Anesthesiology; Co-Chief, Anesthesiology Section, Veterans Administration, Wadsworth.

†Associate Professor, Department of Surgery/Head and Neck.

‡Associate Physician, Department of Anesthesiology.

§University of California at Los Angeles, School of Medicine, Los Angeles, California 90024.

Paper received: 12/15/75

Accepted for publication: 2/25/76

a laryngeal stent, removed 3 weeks after repair. Because of glottic insufficiency, Teflon was injected into the right vocal cord area without appreciable augmentation of the posterior third of the cord. The cord was therefore nonmobile and laterally displaced, especially posteriorly. Since he had difficulty talking and coughing, he was scheduled for removal of a Teflon granuloma of the anterior aspect of the cord and Teflon injection to its posterior part.

The patient received 100 mg of meperidine and 0.5 mg of atropine IM, 1 hour before operation. On his arrival in the operating room, a 16-gauge IV cannula was placed in the left arm and infusion was started. When the blood pressure cuff and ECG leads had been attached, the patient was preoxygenated for 4 minutes with 100% O_2, using a circle system with an inflow rate of 16 L/min. He was given IV fentanyl (0.2 mg) until drowsy; then, thiopental (375 mg), and 80 mg of succinylcholine IV. A 0.2% solution of succinylcholine was infused at about 10 mgms/min. A 14-gauge, 3.8 cm Deseret Radio Opaque Teflon catheter was then inserted through the cricothyroid membrane into the trachea. (This catheter has side holes near the tip, designed originally for venous lines in patients on dialysis.) A 10-ml syringe was attached and air aspirated from the trachea to confirm position. The catheter was connected to a high-pressure jetting system consisting of a Bird high-flow N_2O-O_2 blender, pressure-reducing valve, and a flow-interrupting device.[1] Anesthesia was maintained by intermittent jetting from this catheter with a mixture of N_2O-O_2 (60:40) at a pressure of 30 psi, producing adequate chest expansion with an estimated tidal volume of 800 ml.

As the patient had a relatively short neck, the surgeon extended the patient's head to insert the laryngoscope; in the process, the tip of the cannula was pulled back from its position in the trachea to a position between the cricothyroid membrane and the skin, with resultant expansion of the neck during jetting. Jetting was immediately stopped, while the needle was removed and replaced through the same puncture site with a 5-cm, 14-gauge needle of the same type, and the jetting system was then reattached. Ventilation of the patient was now easily maintained but the neck was still slightly swollen and the characteristic crepitus of subcutaneous emphysema could be felt. On insertion of an operating laryngoscope blade, the surgeon observed a large pneumatocele distending the right aryepiglottic space. This gas was aspirated easily with a 17-gauge needle on a laryngeal syringe. The proposed operation was then completed.

DISCUSSION

This method of management during laryngeal operations has been advocated by various authors.[2-5] However, it is not without complications among which is pneumothorax due to excessive pressure in the lung if jetting is continued with the vocal cords closed or the upper airway obstructed.[6] Air has been injected through the posterior side of the tracheal wall by inadvertently placing a long needle through the other side of the trachea.* This could proceed to mediastinal emphysema and bilateral pneumothoraces.

It is interesting that the gas was able to track through the fascial planes to the area of the vocal cords. The air may have spread cephalad because of fibrosis in the tissues below the site of needle puncture following healing of the tracheostomy. Also the needle puncture was at the cricothyroid membrane rather than between the tracheal rings, which is the more common site.[2-5] The surgeon, however, was easily able to deal with the problem by letting out the air from the swollen area, enabling the patient to regain his normal anatomy.

Since the pressure developed in the lungs is dependent upon the flow of gas from the needle and the resistance to flow is inversely proportional to the length (Hagen-Poiseuille law), a short needle will deliver better ventilation than a long one. We now routinely use 5-cm needles for this technic.

*Grant D: personal communication, 1971.

REFERENCES

1. Carden E, Vest HR: Further advances in anesthetic technics for microlaryngeal surgery. Anesth & Analg 53:584-587, 1974

2. Spoerel WE, Greenway RE: Techniques of ventilation. Br J Anaesth 43:932-939, 1971

3. Chakravarty K, Narayanan PS, Spoerel WE: Further studies on transtracheal ventilation: the influence of upper airway obstruction on the patterns of pressure and volume changes. Br J Anaesth 43:733-736, 1973

4. Smith RB, Myers EN, Sherman H: Transtracheal Ventilation in Pediatric Patients. Br J Anaesth 46:313-314, 1974

5. Smith RB: Transtracheal ventilation during anesthesia. Anesth & Analg 53:225-228, 1974

6. Fenwick DG, Baker R: Communication. Ann Otol (in press)

Acute Ethanol Intoxication and Its Prolonged Effect on a Full-Term Neonate

S. S. KIM, MD*
ROBERT HODGKINSON, MD†
Bronx, New York‡

DURING a double-blind trial of neurobehavioral assessment of neonates, we observed a baby whose depressed performance was subsequently explained by the inadvertent administration of IV ethanol to the mother during labor. This report is presented to: (1) emphasize the need of care in routine IV therapy and (2) review the pharmacologic significance of alcohol with respect to the neonate.

CASE REPORT

A 36-year-old multipara weighing 72.6 kg was admitted in early labor. Her previous medical, surgical, and obstetric history was unremarkable. After 5 hours, her membranes ruptured at 4 cm dilation of the cervix and an IV infusion was started. When, 3 hours later, there was no progress and pelvimetry confirmed cephalopelvic disproportion, cesarean section was decided on. Meperidine (50 mg) and promethazine (25 mg) had been given twice, 8 and 5 hours previously.

On arrival in the operating room, the anesthesiologist noted the extreme drowsiness, disorientation, and nystagmus of the mother. Checking the IV bottle, it was found that almost 700 ml (40 gm) of 5% alcohol had been given in error for lactated Ringer's solution, most of it probably in the previous hour. The patient was induced with 250 mg of thiopental (less than the 4 mg/kg usually given for a crash induction) and 100 mg of succinylcholine, and maintained on a 6-L flow of O_2 until the baby was delivered 5 minutes later. There was no meconium, and fetal heart sounds were stable. As the 1-minute Apgar score was 3 (1=color, tone, and heart rate), the baby's trachea was intubated and 100% O_2 administered with intermittent positive pressure. The 5-minute Apgar was 7 (respiration, response, and color were each 1). The heart rate and tone responded rapidly and the baby was described as vigorous at 10 minutes. The heart rate was 120 and the blood pressure 80/60 2 hours later. The baby's weight was 3000 gm, length 49 cm, and head circumference 34¼ cm. There was no evidence of hypothermia, hypoglycemia, or dehydration at any time.

The Scanlon[1] group of neurobehavioral tests were administered 1 hour before a feed on days 1 through 10 by an investigator (SSK) with no knowledge of the anesthetic management, the method of delivery, or the perinatal risk factors (the fact that alcohol had been administered was not known to the investigators until 48 hours later). The scores were compared with those of 35 other babies delivered by cesarean section and receiving the same amount of thiopental. Fifteen of the mothers had received the same amount or more of meperidine. This baby had a lower score for the overall score (based on the evaluator's assessment performance of all neurobehavioral tests) than any of the other 35 neonates on each of the first 3 days of life.

The subject baby's score for tone, rooting, and alertness were also the lowest in the series for the first 3 days. Eight babies had an equally low sucking score, 5 an equally low Moro reflex score, and 4 an equally low response to sound score for the first 3 days. After the 3rd day, all the baby's scores were normal except for tone, which was intermittently found to be low until the 7th day. The mother and baby were both well and were discharged on the 10th day.

DISCUSSION

The IV administration of alcohol was introduced in 1967 to inhibit premature labor,[2]

*Resident.
†Assistant Professor.
‡Department of Anesthesiology, Albert Einstein College of Medicine, Bronx, New York 10461.

Paper received: 11/10/75
Accepted for publication: 1/22/76

although a recent trial has shown it to be no more effective than a placebo.[3] Use of alcohol to delay labor can be dangerous to both mother and baby. The acidity and volume of maternal gastric secretions are proportionate to the amount of alcohol administered, and subsequent anesthesia has been associated with aspiration of the highly acid secretion, followed by pneumonitis.[4]

Alcohol freely passes through the placenta; an acute withdrawal syndrome[5] has been described, as well as fetal alcohol syndrome[6] (microcephaly, growth retardation, and multiple congenital abnormalities) following chronic alcoholism.

The alcohol dehydrogenase activity in the fetus is only 25% that of the adult,[7] and the rate of disappearance of alcohol from the neonate is probably slower than the mean 7 gm/hr shown by a normal 68-kg adult.[8] In addition to its effect on neurobehavior, alcohol is a potent depressant of hypocapnic and hypoxic drive in man.[9]

In view of its doubtful efficacy in suppressing premature labor, its potent cerebral-depressant effect on the fetus already handicapped by prematurity, and its propensity to produce a highly acid, high-volume gastric secretion in the mother, it is time that the use of IV alcohol be reevaluated. If its use is to be continued, the anesthesiologist should ascertain that alcohol bottles resembling bottles of lactated Ringer's solution are segregated from other infusional fluids, should recognize the increased risk of maternal acid aspiration, and should be prepared to resuscitate a possibly very inebriated neonate.

* * *

Editor's note: A reviewer comments: "Our gastroenterologists are doing clinical research on IV alcohol in normal volunteers and are impressed with the marked increase in gastric secretion and the high incidence of hemorrhagic gastritis."

REFERENCES

1. Scanlon JW, Brown WU, Weiss JB, et al: Neurobehavioral responses of newborn infants after maternal epidural anesthesia. Anesthesiology 40: 121-128, 1974

2. Fuchs F, Fuchs AR, Problete VF, et al: Effect of alcohol on threatened premature labor. Am J Obstet Gynecol 99:627-633, 1967

3. Castren O, Gummerus M, Saarikoski S: Treatment of imminent premature labour. Acta Obstet Gynecol Scand 54:95-100, 1975

4. Greenhouse BS, Hook R, Hehre FW: Aspiration pneumonia following intravenous administration of alcohol during labor. JAMA 210:2393-2395, 1969

5. Nichols MM: Acute alcohol withdrawal syndrome in a newborn. Am J Dis Child 113:714-715, 1967

6. Jones KL, Smith DW, Ulleland CN, et al: Pattern of malformation in offspring of alcoholic mothers. Lancet 1:1267-1272, 1973

7. Pikkarainen P, Raiha NRC: Development of alcohol dehydrogenase activity in the human liver. Pediatr Res 1:165-168, 1967

8. Grollman A, Grollman EF: Pharmacology and Theurapeutics. Seventh edition. Philadelphia, Lea & Febiger, 1970, p 70

9. Sahn SA, Lakshminarayan S, Pierson DJ, et al: Effect of ethanol on ventilatory responses to oxygen and carbon dioxide in man. Clin Sci Mol Med 49:33-38, 1975

We Salute . . . .

Edmond I. Eger, II, M.D.

FEW individuals have made the impact on clinical anesthesia that has Edmond I. Eger, II. His bibliography of more than 150 publications reads like the index of a textbook: anesthetic systems, uptake, elimination, MAC, theories of anesthesia, factors which affect anesthetic requirement, mechanism of action, metabolism, toxicity, and cardiorespiratory effects of anesthesia. Dr. Eger recently compiled his research into an excellent book, *Anesthetic Uptake and Action.**

Ted Eger was born in Chicago September 3, 1930. He attended high school there, graduated from the University of Illinois in 1951, and received his MD degree from Northwestern University Medical School in 1955. He completed an internship at St. Luke's Hospital in Chicago and served his residency in anesthesia with Dr. Stuart C. Cullen at the State University of Iowa. From 1958-1960, Dr. Eger acted as Chief of the Anesthesia and Operative Section, US Army Hospital, Ft. Leavenworth, Kansas. During this period, one of his first studies, "The Factors Affecting the Alteration of Nitrous Oxide in the Circle System," was completed.

In 1960, Dr. Eger joined the Department of Anesthesia at the University of California San Francisco Medical Center, where over the next 8 years he attained the rank of Professor. He currently serves as Vice Chairman for Anesthesia Research at the University of California and maintains an active research program of his own.

Dr. Eger was recipient of an NIH Research Career Development Award from 1961 to 1965. He is active in numerous professional societies, including the ASA and AUA, and is a Diplomate of the American Board of Anesthesiology. He currently is a member of the ASA Committee on Research and also serves as consultant to the US Naval Hospital in Oakland and the VA Hospitals in San Francisco and San Diego.

Ted is a kind and generous man, giving freely of his time, his energy, and his counsel. He has the extraordinary ability to excite young physicians as to the fun and usefulness of research, as evidenced by the fact

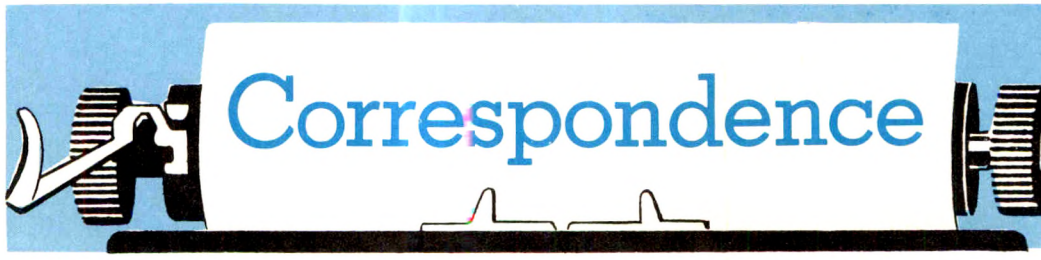
*The Williams and Wilkins Company, Baltimore, Maryland.

that the majority of the 25 research trainees he has supervised have chosen full-time academic careers. He helps young people to "do their own thing." Although he constantly assists them in solving problems and suggests alternative routes, he does not actively compete but rather enables the trainees to mature into satisfied, independent investigators.

Though best known as an investigator, his abilities as a teacher and clinician are also highly regarded. He has made the complex subject of uptake and distribution both understandable and clinically useful. His work on anesthetic systems has been instrumental in teaching us all why we do what we do in the operating room. As a clinician, he possesses the superb attribute of being able to take knowledge from the laboratory and rationally apply it to patient care.

But perhaps that characteristic for which Ted is best loved by those with whom he has worked is his attitude toward people and his approach toward life. He attacks life with the same vigor as he does his work. His interests are widespread, ranging from the love of music and ballet to backpacking and cross-country skiing. Ted, his wife, Dollie, and their four children spend many vacations together traveling, camping, and walking the John Muir Trail.

It is with pleasure and pride that the Editors of *Anesthesia and Analgesia* salute Edmond I. Eger, II, for his many contributions to our specialty.



To the Editor:

In reference to the Questions and Answers section of volume #54, page 211, I wonder if you could be more specific concerning "Nonflammable germicides or detergents . . . to be used when the use of electrosurgery is contemplated," as stated by Paul F. Leonard, M.D., Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota.

A. DelPizzo, M.D., Chairman
Department of Anesthesiology
Hospital of St. Raphael
New Haven, Connecticut

* * *

To the Editor:

In response to Dr. DelPizzo's question: The National Fire Protection Association in its publication 56A "Standard for the Use of Inhalation Anesthetics 1973," states (page 40) that "Inhibited 1,1,1-trichloroethane is a suitable defatting agent." This compound is nonflammable and is biologically inert (not metabolized).

Paul F. Leonard, M.D.
Department of Anesthesiology
Mayo Clinic
Rochester, Minnesota

* * *

To the Editor:

I'm engaged in what seems at times to be a one-man crusade. As an allergist, I'm acutely aware of the life-or-death situations that can be created by insect stings. I've run into several cases where death could have been prevented if an emergency insect-sting kit had been available.

We physicians give insect-sting kits to patients who need them, and we train them in their use. Yet people in positions of responsibility—school nurses or principals, forest rangers, scoutmasters, and others who may encounter people in allergic shock—don't have the kits, nor do they know how to use them. Most state laws prohibit sales of such kits without a prescription. We physicians train our insect-allergy patients to use them, and we see that a kit is available to them. I think state laws should be changed so that persons in the kinds of key positions indicated, after receiving appropriate training, could purchase the kits without prescription. I hope others feel likewise and will be motivated to write their legislators to change the laws.

I would also appreciate hearing from other doctors who know of cases where the use of an insect-sting kit would have prevented death. Write me at: Doctors Park, Building 4-C, Asheville, North Carolina 28801.

Claude A. Frazier, M.D.
Asheville, North Carolina

In each issue of the Journal an article of particular interest and value to anesthesiologists, which has been published elsewhere, will be presented. Primarily the material will contain fundamental basic information which has been presented by anesthesiologists, physiologists, pharmacologists, and others and, on occasion, by commercial firms. In the last instance, these reprintings are not to be construed as an endorsement of the particular commercial firm or its product by Anesthesia and Analgesia—Current Researches.

Treating Acute Heroin and Methadone Toxicity

GEORGE R. GAY, MD, AACT, FAAFP*
DARRYL S. INABA, Pharm. D†

Acute heroin and methadone overdose reactions are seen with increasing frequency in E.R.s servicing middle-class white suburbia. The authors give step-by-step procedures for the management of this life-threatening medical emergency.

FOUR teen-agers carried an unconscious youth into the Haight-Ashbury Free Medical Clinics in San Francisco. He was apneic, cyanotic, and areflexic, but his pulse was strong. His friends said he'd "shot-up with smack"—heroin—just a few minutes before.

Quickly we cleared his mouth of mucus, put an oropharyngeal airway in place, and began mouth-to-mouth respiration. Simultaneously we gave him, I.V., 2 cc naloxone hydrochloride (Narcan) and 5 cc doxapram hydrochloride (Dopram).

The patient's color returned, spontaneous respirations resumed, and he regained full consciousness—all within about 20 seconds. Suddenly he spit out the airway, complaining only of "a terrific headache." We observed him for several hours and then discharged him.

Here at the Haight-Ashbury Clinics we treat well over 400 heroin and methadone addicts a week. Every day we see at least one case of acute toxicity similar to this young man's, and we've yet to lose such an overdose patient—*who had a heartbeat when he arrived.*

Opiate and opioid overdose victims classically present with pinpoint pupils (unless anoxia has caused dilation), areflexia, marked respiratory depression (from apnea to two or three shallow gasping breaths per minute), and a cyanotic, clammy pallor.[1] Always suspect that a comatose patient with questionable or nonexistent history may be such an overdose case.

Treatment, to be effective, must be prompt, and proper measures are essential. Here, in outline form, is the method of emergency therapy we've developed at Haight-Ashbury Clinics:

1. Establish an airway:[2-9]

A. Clean patient's mouth. Mucus, blood, vomitus, gum, or tobacco may be found.

B. With the patient in supine position, tip the head slightly back.[10] Grasping jaw at angles of mandible and at point of chin, draw the head back, chin high, to a "sniffing-like" position, but be careful not to hyperextend. Pull the tongue forward, making sure it isn't occluding the posterior oropharynx. If oropharyngeal reflexes are absent, insert an oropharyngeal or nasopharyngeal

*Former Director of Clinical Activities, Haight-Ashbury Free Medical Clinics, San Francisco, California. Present address: P.O. Box 1169, Mendocino, California 95460.

†Director of Pharmaceutical Services, Haight-Ashbury Free Medical Clinics, San Francisco, California.

Reprinted with permission from Medical Economics, Inc., Oradell, N.J. and the authors.

airway; if one isn't available, hold the tongue forward with your fingers.

C. Breathe for the patient if he or she is apneic—mouth-to-mouth, or mouth-to-nose,[11] or use an Ambu bag if one is handy. If room air is 20 percent oxygen, your mouth-to-mouth respiration will get at least 15 percent oxygen into the patient. Make sure air is entering the lungs—that the chest (not stomach) is expanding. Listen for breath sounds with a stethoscope. Don't stop to look or call for endotracheal equipment—you are dealing with a true emergency and hesitation can spell disaster. Endotracheal intubation should be attempted *only* by a trained anesthesiologist or surgeon—and *only* when the patient has been previously properly oxygenated. You have about two minutes to achieve intubation. If unsuccessful, resume mouth-to-mouth, oxygenating the patient well before attempting intubation again.

2. Quickly assess the cardiovascular system:

A. Check the pulse for rate and rhythm. Check precordial, femoral, temporal, or radial pulses. Don't be lulled into complacency by the strong full pulse of hypoxia, which may be premonitory to terminal arrhythmia and cardiac cessation. Remember: If the patient arrives with a heartbeat, you should be able to save him.

B. Begin external cardiac massage if heartbeat is absent, placing palms of your hands over the patient's lower sternum, depressing firmly 50 times per minute.[12-14] Determine cardiac status with ECG. Institute appropriate action—defibrillation, pacing, etc.

C. In severe cases of narcotics overdose, the patient's cardiovascular system may be so depressed that pulmonary edema develops.[15] Intubation or tracheostomy—plus continuous positive pressure respiration—may be lifesaving.[16,17]

3. Continue treatment for heroin overdose:

A. Give intravenously 2 cc (1 cc/0.4 mg) naloxone hydrochloride. This may be repeated 2 to 3 times at 2 to 3-minute intervals without fear of adverse or agonistic effect (I.V. works in seconds; I.M. administration may take 20 minutes or more to act). If the patient has "collapsed" veins, as many addicts do, try the external jugular or the femoral or inject at the base of the tongue if all else fails.

The Narcan test may be considered to be diagnostic for narcotics overdose; reversing opiate/opioid depressant effects without endangering the patient who may have other depressant drugs in his/her system.

Also, Narcan is free of narcotic agonist effect which *may* be seen with repeated doses of Lorfan or Nalline.

B. Give I.V. 3 to 5 cc (1 cc/20 mg doxapram hydrochloride).[20,21] This is an extremely safe, temporary (lasting 3 to 5 minutes), nonspecific respiratory stimulant. It usually has immediate effect, so be sure airway is open. One word of caution here . . . if prolonged apnea and pre-existing acidosis is suspected, AVOID the use of Dopram, as some hypertensive and metabolic acidotic response may be expected following its use.

C. Stay with the patient until he is fully responsive. If he used a long-acting narcotic, such as methadone hydrochloride (Dolophine), he may lapse back into coma if continuous monitoring is not provided for several hours. With the ever-expanding methadone maintenance programs in this country, providing a continuing increase in street-availability of this government approved highly potent opioid, methadone overdoses are being seen in increasing numbers.

D. If the patient fails to respond, follow established emergency procedures to secure a route for administering I.V. fluids—preferably with a large bore cannula. If moderate to severe acidosis is suspected, administer sodium bicarbonate.[22] Begin the administration of a glucose-electrolyte solution.[23] Draw blood for chemistries. Search for non-overdose etiology—evidence of trauma, blood loss, acute infectious process, and increased intracranial pressure.

E. If long-standing drug depression is suspected (for example, when a patient is discovered unattended), be on guard for atelectasis or pneumonia.[24,25] In any event, hospitalization, vigorous pulmonary therapy, and aggressive antibiotic therapy are indicated.

The typical middle-class junkie—whom you're apt to be treating in increasing numbers—is in his early 20s, white, male (although now up to 35 percent of the clients at the Haight-Ashbury Free Medical Clinics Detoxification Section are female), and an Establishment-alienated dropout from

TABLE

Symptom complex	Treatment
Pain (or expressed somatic discomfiture)	Propoxyphene napsylate (Darvon-N), 200 mg, propoxyphene hydrochloride (Darvon), 130 mg, or pentazocine (Talwin), 100 mg, q 4-6 h.
	Note: Talwin within 12 hours of a "fix" may produce narcotic antagonism creating "instant Cold Turkey" and thus reducing the medication's analgesic effect.
Sleeplessness	Flurazepam (Dalmane) 60 to 90 mg hs, Chloral hydrate, up to 2.5 gr hs.
	Note: At the Haight-Ashbury Detoxification Section we avoid use of the short-acting barbiturates, glutethimide, or methaqualone.
Nervousness	Phenobarbital, 30-60 mg, diazepam (Valium), 5-10 mg., or chlordiazepoxide (Librium), 10 to 25 mg, q 6-8 h.
Gastrointestinal distress	Belladonna leaf extract, phenobarbital (Belphen No. 1), oxyphenonium bromide and phenobarbital (Antrenyl-phenobarbital), or dicyclomine hydrochloride (Bentyl), two capsules q 4 h.
	Note: For pronounced nausea and vomiting, 5-15 mg prochlorperazine (Compazine) q 4 h orally or 10 mg by rectal suppository.

suburbia. He's been on heroin for less than 2 years, but already his habit is demanding up to 20 mg. of pure heroin a day.[26,27] That's more than enough to hide the warning pain of abscessed teeth, pelvic inflammation, or a ruptured appendix.

SHORT-TERM OUTPATIENT OPIATE/OPIOID DETOXIFICATION

Abrupt withdrawal from heroin may be discomfiting in the extreme, but life-threatening crises, such as the convulsions and hyperpyrexia occasionally seen with alcohol-tranquilizer-barbiturate withdrawal, are rare (basically only seen in the premature newborn of the addicted mother). During acute heroin withdrawal the patient may experience hypersalivation, with runny eyes and nose; fever, chills, and diaphoresis; nausea, vomiting, abdominal cramps, and diarrhea; photophobia due to dilation of the pupils; musculoskeletal pains and cramps; jitteriness and insomnia to a marked degree. These symptoms make their appearance from 6 to 8 hours after the last "fix," reaching a maximum at from 24 to 36 hours. Usually withdrawal symptoms subside after 5 days. Insomnia, general irritability, and muscular aches and pains gradually lessen over the ensuing days and weeks. At the Haight-Ashbury Free Medical Clinics, four symptom complexes are commonly treated: pain (muscle, joint, and bone aches), sleeplessness, nervousness, and gastrointestinal complaints.

REFERENCES

1. Eckenhoff JE, Helrich M, Hege MJD, et al: Respiratory hazards of opiates and other narcotic analgesics. Surg Gynec Obstet 101:701-708, 1955

2. Brook MH, Brook J, Wyant GM: Emergency resuscitation. Brit Med J 5319:1564-1565, 1962

3. National Academy of Sciences, National Research Council: Cardiopulmonary resuscitation. JAMA 198:372-379, 1966

4. Cardiopulmonary resuscitation, a Manual for Instructors. New York, American Heart Association, 1967

5. Torpey D, Safar P: Preoperative resuscitation and preparation of the traumatized patient. Int Anesth Clin 6:1041-1119, 1968

6. American Society of Anesthesiologists Committee on Acute Medicine: Recommendations for community-wide emergency medical services. JAMA 204:595-602, 1968

7. Resnoff HL, Safar P: Management of the comatose patient, Respiratory Therapy. Clin Anesth 1:244-258, 1965

8. Pierce EC Jr: Postoperative care. Int Anesth Clin 6:1121-1177, 1968

9. Wylie WD, Churchill-Davidson HC: A Practice of Anaesthesia. Second edition. Chicago, Year Book Medical Publishers, 1966, pp 383-392

10. Greene DG, Elam JO, Dobkin AB, et al: Cinefluorographic study of hyperextension of the neck and upper airway patency. JAMA 176:570-573, 1961

11. Council on Medical Physics of the AMA: Mouth-to-mouth resuscitation. JAMA 167:317-341, 1958

12. Jude JR: Cardiopulmonary resuscitation. JAMA 193:578-679, 1965

13. Jude JR, Kouwenhoven WB, Knickerbocker GG: Cardiac arrest. Report of application of external cardiac massage on 118 patients. JAMA 178:1063-1070, 1961

14. Messer JV: Management of emergencies. XIV. Cardiac arrest. New Eng J Med 275:35-39, 1966

15. Lee JA, Atkinson RS: A Synopsis of Anaesthesia. Fifth edition. Baltimore, Williams & Wilkins Company, 1964, p 586

16. Bjork VO, Engstrom CG: The treatment of ventilatory insufficiency by tracheostomy and artificial ventilation. J Thorac Cardiovasc Surg 34:228-241, 1957

17. Dammann JF Jr: Indications for tracheostomy. Ann NY Acad Sci 121:849-860, 1965

18. Blumberg H, Dayton HB, Wolf PS: Counteraction of narcotic antagonist analgesics by the narcotic antagonist naloxone. Proc Soc Exp Biol Med 123:755-758, 1966

19. Hasbrouck JD: The antagonism of morphine anesthesia by naloxone. Anesth & Analg 50:954-959, 1971

20. Ward JW, Franko BV: A new centrally acting agent (AHR-619) with marked respiratory stimulating, pressor, and "awakening" effects. Fed Proc 21:2325, 1962

21. Canter HG, Luchsinger PC: The treatment of respiratory failure without mechanical assistance. Amer J Med Sci 248:206-211, 1964

22. Malm OJ: Treatment of acidosis and electrolyte disturbances in asphyxia and cardiac arrest. Acta Anaesth Scand 29:165, 1968

23. Shires T: The role of sodium-containing solutions in the treatment of oligemic shock. Surg Clin N Amer 45:365-376, 1965

24. Dripps RD, Deming MV: Postoperative atelectasis and pneumonia. Ann Surg 124:94-110, 1946

25. Dobkin AB: Severe respiratory depression following general anesthesia. Int Anesth Clin 4:609-615, 1966

26. Gay GR, Bathurst W, Matzger AD, et al: Short-term heroin detoxification on an outpatient basis. Int J Addict 6:241-264, 1971

27. Sheppard CW, Gay GR: The changing face of heroin addiction. Int J Addict 6:17-26, 1971

DIABETES AND RESPIRATORY DISTRESS. A retrospective review determined the incidence of respiratory distress syndrome in newborns of diabetic or nondiabetic mothers. The syndrome occurred in 23.4% of the diabetic compared with 1.3% of the nondiabetic group. Therefore, the chance of this syndrome developing in an infant of a diabetic mother is about 24 times that of an infant of a nondiabetic. When all confounding factors were controlled, including the gestational age and route of delivery, the chance of the syndrome developing was still 6 times greater in the diabetic group. Thus, maternal diabetes, per se, probably predispose the infant to respiratory distress. Fetal hypersecretion of insulin may block the enzyme-inductive capability of cortisol which is necessary for lung maturation. *(Robert MF, Neff RN, Hubbell JP et al: Association between maternal diabetes and the respiratory-distress syndrome in the newborn. NEJM 294:357-360, 1976)*

The Physician & The Law

Physician Liability for Death of Heart Transplant Donor Discussed

LEGAL and moral implications of a jury verdict holding a physician not liable for the death of a heart transplant donor were discussed in an article questioning the concept of "brain death."

In the case discussed, the patient had been admitted to a hospital after suffering a massive brain injury. He sustained a later basilar skull fracture on the right side, subdural hematoma on the left, and brain stem contusion.

Emergency surgery was performed and he was placed on a respirator. The treating physician noted that prognosis for recovery was nil and that death was imminent. Shortly thereafter a neurologist obtained an EEG with the results showing "flat lines with occasional artifact."

Vital signs remained about normal for the next two hours, at which time the respirator was cut off. Five minutes later he was pronounced dead, and his heart was removed and transplanted to a recipient.

The patient's brother sued the transplant surgeon for $100,000, alleging that the transplant team engaged in a systematic and nefarious scheme to use the patient's heart and hastened his death by shutting off his mechanical support. The suit also charged that the patient's heart had been removed with only minimal attempts to notify the family and obtain permission.

No opinion was issued in connection with the jury verdict. However, the trial court gave the jury an instruction allowing it to use cessation of brain function as a possible definition of death. The jury found in favor of the transplant surgeon, determining that he had not caused the patient's death by removing him from the respirator after his brain had ceased to function.

The author of the article stated that the principals in the case and the press had treated the case as a "brain death" case. However the determination of when death occurs is a philosophical or moral question,

Reprinted with permission from THE CITATION, published by the Law Division of the American Medical Association.

not a scientific or medical one, the author said. He suggested that the decision as to when the heart may be removed for transplant be made by the patient's relatives, and argued that not consulting them was a serious infringement on the rights of the patient and his family.

He raised the issue of whether this was a "brain death" case or simply a case of stopping treatment of a terminally ill patient. To treat this as a "brain death" case, one must accept several highly questionable premises, including vesting medical professionals with authority to determine life and death. The author also questioned whether the "brain death" concept was intended to apply to death of the entire brain or only of the cortex, which controls consciousness. —*Brain Death,* by Robert M. Veatch, Hastings Center Report, November 1972, p. 10, discussion *Tucker's Administrator v. Lower* (Ct. Law & Eq., Richmond, Va., May 25, 1972).

ANTIBIOTICS. The authors reviewed the records of all surgical patients to determine the incidence of nosocomial (hospital-acquired) infections with or without prophylactic antibiotics. It is estimated that 6.3% of admissions to acute hospitals acquire nosocomial infections. The present study showed that prophylactic antibiotics had no significant effect on the incidence of hospital-acquired infections. *(Finland M, McGowan JE: Nosocomial infections in surgical patients. Observations on effects of prophylactic antibiotics. Arch Surg 111:143-145, 1976)*

Questions and Answers

We invite you to submit questions to the Editorial Office, Kahler East, Suite C, Rochester, Minnesota 55901. The names of those submitting questions will remain anonymous if so desired.

The answers will be prepared by competent authorities, and their names will or will not appear, according to their specific wishes.

Ronald W. Dunbar, M.D.
Contributing Editor
Atlanta, Georgia

* * *

QUESTION: *Is it more dangerous to run a rechargeable ECG monitor (Tektronix®) on a patient while plugged into a grounded circuit than on battery power alone (referring to the electrical hazard)?*

MD, Michigan

ANSWER #1: "Dangerous" here implies a a situation or a device fraught with a clear and present threat to life. A monitor is not "dangerous" merely because the right leg electrode is connected to the chassis and case of the device—as in early production numbers of the type 410 Tektronix (and in many other monitors and ECG machines through the early 1970s). A hazard exists only if the monitor is used on a patient in conjunction with some *other* grossly defective or incorrectly connected piece of equipment. A firm caveat to this effect is found in the excellent instruction book for the Tektronix type 410.

Operation by battery means the patient is no longer connected to ground through the grounding conductor in the power cord. With the type 410 monitor, however, the isolation from ground provided in the battery mode of operation can be defeated if the monitor case is grounded through a grounded support bracket or through an accessory grounding wire.

As a matter of principle, deliberate grounding of patients (and oneself) is to be avoided. Not long ago, though, a grounding connection to the subject was a virtual necessity—and a standard practice—in order to reduce electrical noise on monitors and recorders. Now, with improved circuitry and components, highly effective "dodges" for the noise problem are easily realized without the need to ground the subject. Monitors and ECG machines of recent design, therefore, provide a large value of resistance between every patient-connected electrode and the monitor frame and case. This is accomplished by appropriate electronic design of the "front end" (the input from the patient), and such isolation is wholly independent of whether the machine is power-line operated or in the battery mode of operation.

John M. R. Bruner, MD
Groton, Massachusetts

* * *

ANSWER #2: The simplest answer is YES. That is, in general it is safer to run all (rechargeable) battery-powered monitoring devices completely disconnected from the wall power/grounding system (regardless of whether the power system is a "grounded" circuit or an "isolated" circuit). Also, it is safer NOT to connect such an ECG monitor to another device, such as a writer which is wall powered and/or grounded.

A more complete answer would be very lengthy, since: (1) there are 2 basic types of Tektronix ECG monitors (410 and 408/412), which can be hazardous to patient or anesthetist in different ways and in differing degrees, depending on the particular electrical environment; and (2) detailed consideration of the most probable electrical faults depends on the type of wall power/grounding system (does it come from an isolation transformer or not?).

The initial answer (yes, it is more dangerous) is especially true with the type 410 (oldest model), due mainly to the relatively low resistance between the right leg lead and wall ground if the monitor is plugged in. In the type 408/412, the patient is highly isolated from the wall power/grounding system even if the monitor is plugged in; it is therefore much safer to operate the 408/412 in this way than it is the 410.

When using the type 410 with a patient who can come in contact with a high-voltage power source (a faulty cautery, defibrillator, or other line-powered device), electrical danger to the patient or anesthetist (such as a cautery burn at the right leg electrode) is minimized by the following: (1) disconnect the power cord from the monitor and the wall; (2) do not connect the case-grounding jack (on the side) to a grounded point; and (3) make sure that none of the metal surfaces of the monitor's base or mounting bracket are touching a grounded surface (such as a metal table or pole mounted on conductive wheels in contact with a conductive floor).

Wesley T. Frazier, MD
A. William Paulsen, MMSc
Division of Instrumentation and Monitoring
Department of Anesthesiology
Emory University School of Medicine
Atlanta, Georgia

* * *

QUESTION: *Is the ASA classification of risk considered surgical risk or anesthetic risk?*

MD, Missouri

ANSWER #1: First, there is no ASA classification of risk; there is a classification of physical status (PS), suggested for grading or rating the preoperative condition of patients based on the amount and/or severity of disease present.

Saklad,[1] in 1941, presented a classification for physical status containing 6 categories, 4 basic, PS 1 through 4, plus 2 additional ones, PS 5 and 6, that were combinations of the basic ones to be used when a patient was to undergo an emergency procedure. At some point between 1941 and 1944, another category, PS 7, for the patient who was moribund, was added to the classification. Waters and Gillespie[2] used this classification of physical status, and then Dripps' group,[3] in 1961, modified the classification, by using PS 5 as the category for the moribund patient, eliminating PS 6 and 7 and designating emergency status by using the letter E along with the basic PS of the patient. It has remained unchanged since that time.[4,5]

The judgment as to the degree of risk to the patient from the surgical procedure or the anesthetic depends on circumstances. Some years ago it was recognized, and probably it is even more true today, that risk from operation involved many variables or intangibles that could not be precisely defined in such a way as to permit evaluation of surgical risk. Collins[6] noted that these variables fall into 3 categories: (1) those related to the patient; (2) factors related to the surgical procedure and operating conditions; and (3) anesthetic considerations. Because it was felt that only the patient, with his individual variations, was the single constant factor in the picture, the consideration was given to a classification for the patient based upon his physical condition at the time he presented for operation.

The presently published ASA classifications carry brief descriptions, considerably less detailed than in Saklad's original work, Dripp's group related the PS assigned preoperatively with aspects of postoperative mortality. Analysis of the surgical and anesthetic factors for determining the total operative risk is well presented by Saklad and by Dripps. Another variable of importance, usually neglected in such reviews, is the matter of the time taken for the procedure, which may be critical for any patient.

There does not seem to be a concise answer to the question of what is anesthesia risk and what is surgical risk. The problem really is risk for the patient that arises from the combination of surgery and anesthesia. Preoperative classification of patients according to PS is a valuable tool for the anesthesiologist but is not absolute for any patient at all times. In general, the patient who is classified as PS 1 or 2 usually will tolerate the anesthesia and operation better than those rated as PS 3 through 5, but such a determination does not guard the patient against unforeseen complications or surgical and/or anesthetic errors.

Robert T. Capps, MD
Portland, Oregon

REFERENCES

1. Saklad M: Grading of patients for surgical procedures. Anesthesiology 2:281-284, 1941

2. Waters RM, Gillespie NA: Deaths in the operating room. Anesthesiology 5:113-128, 1944

3. Dripps RD, Lamont A, Eckenhoff JE: The role of anesthesia in surgical mortality. JAMA 178:261-266, 1961

4. Summary of Proceedings of House of Delegates, American Society of Anesthesiologists, 507-1.1, p 1, 1962

5. New Classification of Physical Status. Anesthesiology 24:111, 1963

6. Collins VJ: Principles of Anesthesiology. Philadelphia, Lea & Febiger, 1966

ANSWER #2: Neither! The ASA classification relates to the physical status (PS) of the patient and not to risk imposed by surgery or anesthesia.

In 1941, the ASA empowered a committee to devise a system for the collection and tabulation of data in anesthesia. Saklad, the chairman, stated that it was necessary to set arbitrary definitions of variables.[1] At the time, "operative risk" was one of the variables often considered, and this assessment encompassed a number of factors, including condition of the patient, operative procedure, skill of the surgeon, experience of the anesthetist, postoperative care, etc. It thus became evident that assignment of "operative risk" to a patient involved many intangible variables peculiar to the circumstances prevailing at that moment. This committee, therefore, proposed a classification of physical state of the patient, per se, with no attempt to prognosticate the influence of a surgical procedure or anesthesia. The original proposal encompassed 6 PS classes, the latter two relating to emergency procedures.

In 1962, the ASA Committee on Clinical Anesthesia Study Commissions proposed a revision of this classification to encompass 5 PS classes, each to be preceded with an "E" in the event of an emergency operation.[2] The ASA House of Delegates accepted this proposal (resolution 6) at its annual meeting in 1962. The transaction was reported[3] in 1962 and also[4] in 1963. The format has continued as the accepted model for PS classification.

Otto C. Phillips, MD
Division of Anesthesiology
Western Pennsylvania Hospital
Pittsburgh, Pennsylvania

REFERENCES

1. Saklad M: Grading of patients for surgical procedures. Anesthesiology 2:281-284, 1941

2. Committee on Clinical Anesthesia Study Commissions, Annual Report. ASA Handbook for House of Delegates, 507-1.1, p 1, 1962

3. New Classification of Physical Status. ASA Newsletter, December 1962

4. New Classification of Physical Status. Anesthesiology 24:111, 1963

* * *

QUESTION: *Would heavy exposure to anesthetic gases (halothane and methoxyflurane) over a period of about 1 month have any effect on the Breathalyzer test given by law-enforcement officers?*

MD, Connecticut

ANSWER #1: The standard Breathalyzer test for alcohol in exhaled air uses the dichromate oxidation of alcohol to acetic acid in sulfuric acid.[1] In principle, this test will respond to any oxidizable molecule in the breath. However, in practice, the rate of oxidation is too slow for any species to be detected except alcohols and aldehydes. The response of alcohols is twice the response of aldehydes, and the relevant concentration in breath is several hundred parts per million (ppm). The halogenated hydrocarbon and halogenated ether anesthetics are present in end-expired breath in concentrations below 1 ppm following routine occupational exposure.

Since the breath concentrations of these anesthetics is so low and they are less reactive than alcohol, they should have no noticeable effect on the Breathalyzer test.

Thomas H. Corbett, MD
Research Services
USVA Hospital
Ann Arbor, Michigan
and
Donald H. Stedman, PhD
Department of Chemistry
University of Michigan
Ann Arbor, Michigan

REFERENCE

1. Alcohol and the Impaired Driver. Committee of Medicolegal Problems, American Medical Association, 1970

* * *

ANSWER #2: The Breathalyzer test detects the presence of ethanol vapors in the exhaled alveolar air of a suspected drunk driver. The essential reaction is an oxidation of ethanol, converting a colored dichromate solution to a nearly colorless reduced form of chromate in the presence of sulfuric acid. The color difference is quantitated by colorimetry.

The reaction is not specific for ethanol. Acetone, ether, and paraldehyde can interfere or give false-positive readings. Blood concentrations of 100 to 125 mg % of diethyl ether are required for a positive reaction in the Breathalyzer, according to a personal communication from LG Porter, Supervisor, Alcohol Testing, Approval and Permit Program, Ohio Department of

Health. Such blood concentrations of diethyl ether are anesthetic and will not be encountered in someone who is able to drive. We believe that the biotransformation of diethyl ether to ethanol contributes to the positive Breathalyzer test during ether anesthesia.

Only minute, albeit persistent, amounts of volatile anesthetics are exhaled after OR work. Methoxyflurane concentrations of less than 1 ppm have been found in the exhaled air of anesthesiologists for as long as 30 hours after giving methoxyflurane anesthesia,[1] and halothane is exhaled for at least 6 days after exposure to trace concentrations.[2]

The effect of occupational exposure to halothane and methoxyflurane on the Breathalyzer test is not known. When determining the degree of exposure from post-exposure analysis of breath, 4 variables must be considered: concentration, length of exposure, amount in breath after exposure, and period of time after exposure. Taking these factors into consideration, it is unlikely that more than 10 ppm of halothane and more than 1 ppm of methoxyflurane can be found on the breath of an anesthesiologist driving a car.

To determine whether such concentrations of halothane or methoxyflurane can give a reading on the Breathalyzer test, we prepared these samples: halothane 1 ppm and enflurane 1 ppm, halothane 10 and 100 ppm, and methoxyflurane 1 ppm, diluted in room air, injecting 30 ml of each into the Breathalyzer. In no case was a color change seen in the reagent solution.

R. L. Hall, MD
H. F. Cascorbi, MD, PhD
Department of Anesthesiology
Case Western Reserve
University Hospitals
Cleveland, Ohio

REFERENCES

1. Whitcher CE, Cohen EN, Trudell JR: Chronic exposure to anesthetic gases in the operating room. Anesthesiology 35:348-353, 1971

2. Cascorbi HF, Blake DA, Helrich M: Differences in biotransformation of halothane in man. Anesthesiology 32:119-123, 1970

IN THE NEXT ISSUE

Scientific Articles

Sept.-Oct., 1976

RELATION OF $Paco_2$ TO FRESH GAS FLOW IN A CIRCLE SYSTEM—Kanchan Patel, M.D., Edward J. Bennett, M.D., Ernest M. Grundy, F.F.A.R.C.S., and Artemio Ignacio, Jr., M.D., Chicago, Illinois.

SODIUM NITROPRUSSIDE-INDUCED HYPOTENSION FOR SUPINE TOTAL HIP REPLACEMENT—Noel W. Lawson, M.D., Dola S. Thompson, M.D., Carl L. Nelson, M.D., Joan W. Flacke, M.D., and Edward R. North, M.D., Little Rock, Arkansas.

CHANGE IN PULMONARY VENOUS ADMIXTURE WITH VARYING INSPIRED OXYGEN—Michael E. Douglas, Major, USAF (MC), John B. Downs, M.D., Francis J. Dannemiller, Colonel, USAF (MC), Michael R. Hodges, and Edwin S. Munson, M.D., Lackland AFB, Texas and Gainesville, Florida.

MAINTENANCE OF BODY TEMPERATURE BY HEATED HUMIDIFICATION—Henry C. Tausk, M.D., Raymond Miller, M.D., and Robert B. Roberts, M.D., New York, New York.

MASSIVE MYOGLOBINURIA PRECIPITATED BY HALOTHANE AND SUCCINYLCHOLINE IN A MEMBER OF A FAMILY WITH ELEVATION OF SERUM CREATINE PHOSPHOKINASE—William E. Moore, M.D., Robert L. Watson, M.D., and James J. Summary, Ph.D., Honolulu, Hawaii.

EPIDEMIOLOGIC ANSWERS TO LABORATORY QUESTIONS IN ENVIRONMENTAL CANCER — Irving J. Selikoff, M.D., New York, New York.

PANEL:

ANESTHESIA FOR THE PATIENT WITH CARDIAC DISEASE—Emerson A. Moffitt, M.D., Halifax, Nova Scotia, Canada.

PREOPERATIVE EVALUATION OF THE PATIENT WITH HEART DISEASE — Alan H. Goldberg, M.D., Boston, Massachusetts.

ANESTHETIC MANAGEMENT—Wendell C. Stevens, M.D., San Francisco, California.

DRUGS IN CARDIAC SUPPORTIVE CARE—Roger D. White, M.D., Rochester, Minnesota.

ANESTHESIA FOR PATIENTS WITH PACEMAKERS—J. Earl Wynands, M.D., Montreal, Quebec, Canada.

ANESTHESIA AFTER RECENT INFARCTION—Emerson A. Moffitt, M.D., Halifax, Nova Scotia, Canada.

HALOTHANE MAC IN DOGS UNCHANGED BY PHENOBARBITAL—Oscar Viegas, M.D., and Robert K. Stoelting, M.D., Indianapolis, Indiana.

A PREPLANNED TREATMENT FOR MALIGNANT HYPERPYREXIA—John C. Fraser, M.D., Robert S. Crumrine, M.D., and Robert J. Izant, Jr., M.D., Cleveland, Ohio.

CLINICAL USE OF ETOMIDATE FOR ANESTHESIA INDUCTION: A PRELIMINARY REPORT—Robert J. Fragen, M.D., Nancy Caldwell, CRNA, and Edward A. Brunner, M.D., Ph.D., Chicago, Illinois.

HYPERTENSION AND DECREASED RENAL BLOOD FLOW FOLLOWING METHYLENE BLUE INJECTION—Alexander A. Birch, M.D., and William H. Boyce, M.D., Winston Salem, North Carolina.

EFFECT OF MORPHINE-DIAZEPAM ON AWARENESS AND DREAMS OF PATIENTS UNDER NITROUS OXIDE ANESTHESIA FOR CESAREAN SECTION—Ezzat Abouleish, M.B., and Floyd H. Taylor, Sc.D., Pittsburgh, Pennsylvania.

ABSENCE OF RECALL AFTER GENERAL ANESTHESIA: IMPLICATIONS FOR THEORY AND PRACTICE — Stephen L. Dubovsky, M.D., and Robert Trustman, Ph.D., Denver, Colorado.

ANESTHESIA FOR VANISHING LUNG SYNDROME: REPORT OF A CASE — Nelson Isenhower, M.D., and Roy F. Cucchiara, M.D., Rochester, Minnesota.

NEUTROPHIL CHEMOTAXIS DURING AND AFTER GENERAL ANESTHESIA AND OPERATION—Theodore H. Stanley, M.D., Harry Hill, M.D., and Gary E. Hill, M.D., Salt Lake City, Utah.

THE EFFECTS OF HEPARIN ON RECOVERY FROM ISCHEMIC BRAIN INJURIES IN CATS—Edward H. Stullken, M.D., and Martin D. Sokoll, M.D., Iowa City, Iowa.

ADVANCES IN PREANESTHETIC EVALUATION AND MANAGEMENT OF MALIGNANT HYPERTHERMIA IN THE EXPERIMENTAL MODEL—Charles E. Short, D.V.M., Robert R. Paddleford, D.V.M., Charles J. McGrath, D.V.M., and Charles H. Williams, Ph.D., Columbia, Missouri.

EARLY REVERSAL OF POSTOPERATIVE HYPOXEMIA—A. Eugene Pflug, M.D., Michael J. Lindop, M.D., Terrance M. Murphy, M.D., Geordis M. Aasheim, M.D., and Harold A. Beck, B.S., Seattle, Washington.

A COMPARATIVE INTERACTION OF EPINEPHRINE WITH ENFLURANE, ISOFLURANE AND HALOTHANE IN MAN—Richard R. Johnston, M.D., Edmond I. Eger II, M.D., and Charles Wilson, M.D., San Francisco, California.

TRAIN-OF-FOUR FADE AND EDROPHONIUM ANTAGONISM OF NEUROMUSCULAR BLOCK BY SUCCINYLCHOLINE IN MAN—Chingmuh Lee, M.D., Torrance, California.

THOUGHTS ABOUT MEDICAL WRITING—Charles G. Roland, M.D., Rochester, Minnesota.

CASE HISTORY #92: PROLONGED APNEA AFTER SUCCINYLCHOLINE IN A DENTAL OUTPATIENT — Richard G. McLaren, M.D., and Emerson A. Moffitt, M.D., Halifax, Nova Scotia, Canada.

BRIEF REPORTS:

A PEEP DEVICE FOR A MANUAL BAG VENTILATOR—Azriel Perel, M.D., Dan Eimerl, M.D., and Morris Grossberg, IRIT, Jerusalem, Israel.

A SAFETY VALVE FOR THE PEDIATRIC REES SYSTEM—Sivam Ramanathan, M.D., Jack Chalon, M.D., and Herman Turndorf, M.D., New York, New York.

HAZARDS OF DISPOSABLE REBREATHING CIRCUITS—James E. Cottrell, M.D., William Bernhard, M.D., and Herman Turndorf, M.D., New York, New York.

THE TRACHEAL BRONCHUS: AN UNUSUAL AIRWAY PROBLEM — Tameriisa Venkateswarlu, M.D., Cecil J. Turner, M.D., James D. Carter, M.D., and Dean H. Morrow, M.D., Houston, Texas.

A PRECORDIAL ECG LEAD FOR CHEST OPERATIONS—Brian Dalton, M.D., Boston, Massachusetts.

INNOMINATE ARTERY COMPRESSION SIMULATING CARDIAC ARREST DURING MEDIASTINOSCOPY: A CASE REPORT —Jae-Hwan Lee, M.D., and Anthony Salvatore, M.D., White Plains, New York.

A Guide for Authors

Anesthesia and Analgesia . . . Current Researches invites manuscripts on subjects pertinent to the specialty of Anesthesia.

Send manuscripts and illustrations in *triplicate* to:

T. H. Seldon, MD, Editor
Kahler East, Suite C
Rochester, Minnesota 55901

Four categories of reports will be considered for publication.

1. Original articles describing clinical or laboratory research.

2. Brief Reports describing new anesthetic technics, equipment, clinical, or laboratory studies.

3. Case Reports.

4. Letters-to-the-Editor.

EDITORIAL POLICIES

Peer review.—All papers submitted are reviewed by selected referees with respect to validity, pertinence, completeness, and originality. If accepted for publication, editorial revisions may be made to aid clarity and understanding. Edited copy will be submitted to authors for approval before the paper goes to the printer. Pageproofs also will be submitted to the authors for final approval. Reprint order forms will accompany pageproofs.

Cover letter.—A letter must accompany each manuscript, stating that the work has not been simultaneously submitted to another journal or previously published in part or whole. The name and address of the author to whom correspondence may be directed should be given.

Legal and ethical considerations.—Information or illustrations which might permit identification of patients must not be used.

Reports describing data from experiments performed on humans must contain a statement in the Methods section, when appropriate, that written informed consent and/or institutional approval of the investigation has been obtained, and that procedures involving the use of animals was conducted so as to minimize discomfort.

Excerpts from material published elsewhere must be accompanied by written permission from the author and publisher to reproduce the material.

JOURNAL STYLE

Format.—All portions of the manuscript should be typewritten and double-spaced, including lists of reference citations. Each component of the paper (title page, with authors' academic rank and addresses, Introduction, Methods, Results, Discussion, References, Legends) should begin on a separate page. Original articles must be preceded by an Abstract concisely describing the purpose, methods, results, and conclusions. Abstracts should not exceed 1 typewritten page in length. Brief Reports and Case Reports do not require an Abstract, but a Summary at the end may be appropriate.

Original articles should be concise (not over 3000 words) and present new information pertinent to anesthesia. Preliminary reports or fragments of material that may better be included in a single, more detailed, report should not be submitted. Brief Reports describing new equipment or technics should present new advances, with advantages over the alternatives. Descriptions of new equipment must be sufficient to permit the reader to either construct or purchase the equipment. Case Reports should emphasize important clinical conditions or variations in typical patient responses. Letters-to-the-Editor must be brief (250-500 words) and should offer constructive comments on

recently published articles or discuss areas of general interest to anesthesiologists.

Measurement units.—The metric system should be used for all such data as length, mass, volume, and temperatures. Torr should be used in place of mm Hg for partial pressures. Authors are encouraged to adopt the International System of units (moles per liter rather than mg percent) for concentrations or amounts of substances. (See Padmore GRA, Nunn JF: SI Units in relation to anaesthesia. A review of the present position. Br J Anaesth 46:236-243, 1974).

Drug names.—Generic or chemical drug names are required. Brand names may be inserted in parentheses after the generic name, if pertinent.

Abbreviations.—The first time an abbreviation appears it should be preceded by the full word it represents.

Respiratory symbols.—Symbols for respiratory physiology should be defined the first time used and should follow Pappenheimer J et al: Standardization of definitions and symbols in respiratory physiology. Fed Proc 9:602-605, 1950.

References.—References should correspond to Index Medicus style and should be listed in the same numerical order as they appear in the text. Reports that are not accessible to all readers or that have not undergone editorial review (abstracts, correspondence, or personal communications) should not be included in numerical listings but may be footnoted. They should include pertinent addresses as well as source and authors' names.

Illustrations.—Drawings and photographs (unmounted glossy prints) should be numbered in order of appearance in the manuscript and labeled on the back with the first author's name and indicate the top edge of the picture.

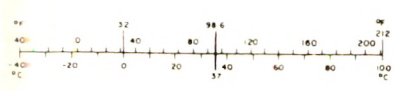
Tables.—These should carry a title or caption and should supplement, not duplicate, the text.

Metric Conversion

HEIGHT			WEIGHT	
Cm	Feet	Inches (approx.)	Kilograms	Pounds
15	0 ft.	6 in.		
30	1 ft.	0 in.	1	2.2
45	1 ft.	8 in.	5	11
60	1 ft.	11½ in.	10	22
75	2 ft.	5½ in.	15	33
105	3 ft.	5 in.	20	44
115	3 ft.	9 in.	25	55
120	3 ft.	11 in.	30	66
125	4 ft.	1 in.	35	77
130	4 ft.	3 in.	40	88
135	4 ft.	5 in.	45	99
140	4 ft.	7 in.	50	110
145	4 ft.	9 in.	55	121
150	4 ft.	11 in.	60	132
155	5 ft.	1 in.	65	143
160	5 ft.	3 in.	70	154
165	5 ft.	5 in.	75	165
170	5 ft.	7 in.	80	176
175	5 ft.	9 in.	85	187
180	5 ft.	11 in.	90	198
185	6 ft.	1 in.	95	209
190	6 ft.	3 in.	100	220
195	6 ft.	5 in.	105	231
200	6 ft.	7 in.	110	242
205	6 ft.	9 in.	115	253
210	6 ft.	11 in.	120	264
215	7 ft.	1 in.	125	275

APPROXIMATE CONVERSIONS FROM METRIC MEASURES

Symbol	When You Know	Multiply by	To Find	Symbol
	LENGTH			
mm	millimeters	0.04	inches	in
cm	centimeters	0.4	inches	in
m	meters	3.3	feet	ft
m	meters	1.1	yards	yd
km	kilometers	0.6	miles	mi
Symbol	When You Know	Multiply by	To Find	Symbol
	MASS (weight)			
g	grams	0.035	ounces	oz
kg	kilograms	2.2	pounds	lb
t	tonnes (1000 kg.)	1.1	short tons	
Symbol	When You Know	Multiply by	To Find	Symbol
	TEMPERATURE (exact)			
°F	Fahrenheit temperature	5/9 (after subtracting 32)	Celsius temperature	°C



A "quick recovery" anesthetic for short surgical procedures

Ethrane® (enflurane) fulfills your anesthetic requirements for short surgical procedures.

Fast Induction, Rapid Recovery. The low blood/gas partition coefficient of ETHRANE (1.91 at 37°C) assures rapid patient induction with minimal excitation. Its mild, pleasant odor is highly acceptable and ETHRANE does not stimulate increased salivation or affect bronchomotor tone.[1] Pharyngeal and laryngeal reflexes can be quickly and easily obtunded. Following anesthesia, because of its low blood solubility, ETHRANE is promptly eliminated at the lungs permitting rapid emergence and recovery.[2]

Stable Cardiac Rhythm. Cardiac rhythm usually remains normal during ETHRANE anesthesia and is not altered even with elevations in arterial carbon dioxide.[3] Although nodal or atrial arrhythmias occasionally appear, ventricular extrasystoles are rare. Heart rate is sustained at preanesthetic levels. Bradycardia or tachycardia do not normally occur. Blood pressure tends to be reduced with induction, but this effect is reversed with surgical stimulation.[4]

Excellent Muscle Relaxation. At clinical concentrations, ETHRANE usually provides muscle relaxation sufficient for lower abdominal procedures. In addition, relaxation is often adequate for procedures of the upper abdomen. If greater relaxation is required, its potentiation of nondepolarizing relaxants reduces the dosage of such adjunctive neuromuscular blocking agents.[4]

Few Anesthetic Aftereffects. Following cessation of anesthesia with ETHRANE, recovery is rapid, uneventful, and complete. Postoperative return of adequate pulmonary ventilation is rapid.[1] Nausea, vomiting, and delirium are rare. Usually there is an early return of lucidity, desire for fluids, and generally a feeling of well-being.[1-4]

WARNING: Motor activity exemplified by movement of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia. For additional warnings, contraindications, and precautions, see following page.

Films Available for Medical Education. As a service to the anesthesia profession, Ohio Medical Products has available, without charge, motion pictures for use in continuing medical education. Topics include such areas as "Management of Ambulatory Surgical Procedures" and "The Use of ETHRANE." To arrange for a personal or group showing, contact your OHIO Anesthetic Representative, or write to our Communications Department in Madison, Wisconsin.

Ethrane®
(enflurane)

Versatile in Concept–Versatile in Performance

Ohio Medical Products
3030 AIRCO DRIVE
MADISON, WISCONSIN 53701

AIRCO®

See following page for full disclosure

Ethrane® (enflurane) Versatile in concept... Versatile in performance.

CAUTION: Federal Law Prohibits Dispensing without Prescription

Description: ETHRANE (enflurane) is a nonflammable anesthetic agent. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether, and its structural formula is:

Some physical constants of the compound are:

Molecular weight	184.5
Boiling point 760 mm Hg.	56.5°C
Refractive index n_D^{20}	1.3026-1.3030
Specific gravity 25°/25°C	1.517
Vapor pressure in mm Hg.**	20°C 174.5 25°C 217.7 36°C 345.2

**Equation for calculation of enflurane vapor pressures:

$$\log_{10} P = A + \frac{B}{T}$$

A = 7.967
B = −1678.4
T = °C + 273.16 (Kelvin)

Partition coefficients @ 37°C	
Water-gas	0.82
Blood-gas	1.91
Oil-gas	98.5
Partition coefficients @ 25°C— rubber and plastic	
Conductive rubber	74.0
Butyl rubber	90.0
Polyvinylchloride	120.0
Polyethylene	≈2.0
Polyurethane	≈1.5
Polyolefin	≈1.2
Butyl acetate	≈3.0
Solubility of enflurane in H_2O at 22°C	0.275%
Solubility of H_2O in enflurane	0.13%
Purity by gas chromatography	>99.9%
Flammability in air	None
Flammability in oxygen (Entire concentration range to saturation at 71 and 113°F and 743 mm Hg. pressure.)	None
M.A.C. (Minimum alveolar concentration)	
Man with pure oxygen	1.68
Man with 70% nitrous oxide	0.56 (est.)

ETHRANE is a clear, colorless, stable liquid without added chemical stabilizers. ETHRANE has a mild, sweet odor. Storage of samples in indirect sunlight in clear, colorless glass for a five year period, as well as direct exposure for 30 hours to a 2 amp, 115 V., 60 cycle long wave U.V. light, produced no changes in composition detectable by gas chromatography. ETHRANE in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed none of the alkali, indicative of strong base stability. ETHRANE does not decompose in contact with soda lime. ETHRANE does not attack aluminum, tin, brass, iron or copper.

Actions: ETHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ETHRANE are rapid. ETHRANE does not appear to stimulate excess salivation or tracheobronchial secretions, or affect bronchomotor tone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ETHRANE. ETHRANE reduces ventilation as depth of anesthesia increases. ETHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm. ETHRANE sensitizes the myocardial conduction system to epinephrine in dog and can produce serious arrhythmias. Comparable information in man is not available.

Muscle relaxation is adequate for intra-abdominal operation at normal levels of anesthesia. Should greater relaxation be necessary, minimal doses of muscle relaxants may be used. All commonly used muscle relaxants are compatible with ETHRANE. **The nondepolarizing muscle relaxants are markedly potentiated.** Neostigmine does not reverse the direct effect of ETHRANE.

Biotransformation of ETHRANE (enflurane) in man results in low levels of serum fluoride ions averaging 15 mM/L. These levels are well below the 50 mM/L seen to produce renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation.

Indications: ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

Contraindications: Seizure disorders (see WARNINGS).

Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.

Warnings: Increasing depth of anesthesia with ETHRANE (enflurane) produces a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by hyperventilation producing low arterial carbon dioxide tension. The pattern serves as a warning that depth of anesthesia is excessive. Cerebral blood flow and metabolism studies in normal volunteers during seizure patterns show no evidence of cerebral hypoxia, and recovery appears to be uncomplicated.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. With deep levels of anesthesia, more marked hypotension and respiratory depression are encountered.

The action of nondepolarizing relaxants is augmented by ETHRANE. Less than the usual amounts of these drugs should be used. The time for recovery from the myoneural effect of these relaxants is greater in the presence of ETHRANE than for other commonly used anesthetics.

The safety of the use of epinephrine topically and subcutaneously has not been established in man.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

Precautions: Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ETHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ETHRANE.

Adverse reactions: 1. Motor activity exemplified by movement of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia. 2. Hypotension and respiratory depression have been reported. 3. Arrhythmias, shivering, nausea, and vomiting have been reported. 4. Elevation of the white blood count has been observed. It has not been determined whether this is related to ETHRANE or to surgical stress.

Dosage and administration: The concentration of ETHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ETHRANE;
b) vaporizers from which delivered flows can easily and readily be calculated.

Maintenance concentration should not exceed 3%. Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ETHRANE and the heart rate remains constant. The use of anticholinergic drugs is a matter of choice.

Induction: Induction may be achieved using ETHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ETHRANE mixture. In general, inspired concentrations of 3.5-4.5% ETHRANE produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be attained with 1.5-3.0% concentration. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm range is preferred to hyper- or hypoventilation in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ETHRANE concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration; establish that the airway is clear and initiate assisted or controlled ventilation with pure oxygen as circumstances dictate.

Administration equipment: ETHRANE (enflurane) may be administered from a flow-through type vaporizer manufactured and specifically calibrated for ETHRANE. Vaporizers which deliver saturated vapor at reasonable flows but are not specifically calibrated for ETHRANE may be used.

ETHRANE contains no stabilizer. Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Packaging: ETHRANE (enflurane) is packaged in 125 and 250 ml. amber bottles. No additives or stabilizers are present.

References:

1. Dobkin, A. B., et al: Ethrane (Compound 347) Anesthesia: A Clinical and Laboratory Review of 700 Cases. Anesthesia and Analgesia **48**:477-494, May-June, 1969.

2. Torri, G., et al: Uptake and Elimination of Enflurane in Man. A Comparative Study between Enflurane and Halothane. British Journal of Anaesthesia. **44**:789-794. August, 1972.

3. Marshall, B.E., et al: Some Pulmonary and Cardiovascular Effects of Enflurane (Ethrane) Anesthesia with Varying $PaCO_2$ in Man. British Journal of Anaesthesia. **43**:996-1002, November, 1971.

4. Botty, C., et al: Clinical Experiences with Compound 347, A Halogenated Anesthetic Agent. Anesthesia and Analgesia **47**:499-505, September-October, 1968.

5. Lebowitz, M.H., et al: Clinical Investigation of Compound 347 (Ethrane). Anesthesia and Analgesia. **49**:1-10, January-February, 1970.

THE VULNERABLE EYE.

Lacri-Lube® protects the vulnerable eye of the anesthetized patient.

The under-protected eye is threatened during general anesthesia. Tape alone can leave your patient's eye vulnerable to dehydration and corneal erosion. And with medicated ointments, you unnecessarily risk allergic reactions and possible long-term sensitization.

Lacri-Lube meets your need for a safer, more sophisticated method of protecting and lubricating the eye. Either on its own or as an adjunct to taping. It's the first non-medicated, sterile ophthalmic ointment specifically designed to lubricate and protect the eye — and do nothing more.

In fact, ophthalmologists have established Lacri-Lube as their lubricant-protectant of choice whenever an eye is jeopardized by exposure or dehydration. And the rapid increase in its surgical use indicates that Lacri-Lube fulfills the same need among anesthesiologists.

Lacri-Lube is the ophthalmic for anesthesia.

When you consider the alternatives, you can't make a better choice.

ALLERGAN
Irvine, CA 92664

ANTILIRIUM
(Physostigmine Salicylate)

REVERSES MOST POST-OPERATIVE DELIRIUM AND PROLONGED SOMNOLENCE

Before prescribing, please consult complete product information, a summary of which follows:

ACTION: ANTILIRIUM (physostigmine salicylate) is a salicylic acid derivative of an alkaloid extracted from seeds of Physostigma Venenosum (calabar bean). The action of the parasympathetic nerves is intermediated by the formation of acetylcholine at the peripheral end of these nerves. Physostigmine inhibits the destructive action of cholinesterase and thereby prolongs and exaggerates the effect of the acetylcholine.

Physostigmine contains a tertiary amine and easily crosses the blood brain barrier, while neostigmine contains a quaternary amine and is not capable of crossing the structure. This may explain why neostigmine does not cause reversal of anticholinergic-induced delirium while physostigmine does.

INDICATIONS: TO REVERSE THE TOXIC EFFECTS UPON THE CENTRAL NERVOUS SYSTEM CAUSED BY DRUGS IN CLINICAL OR TOXIC DOSAGES CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING.

SEVERE ANTICHOLINERGIC POISONING MAY PRODUCE: COMA, MEDULLARY PARALYSIS AND DEATH.

CENTRAL TOXIC EFFECTS MAY INCLUDE: HALLUCINATIONS, DELIRIUM, DISORIENTATION, ANXIETY AND HYPERACTIVITY.

Dramatic reversal within minutes of coma, hallucinations, and other signs can be expected if the diagnosis is correct and the patient has not suffered anoxia or other insult. Therapeutic doses may be necessary at intervals as life-threatening signs recur. Physostigmine is destroyed in the body in 60 to 120 minutes.

CONTRAINDICATIONS: Physostigmine should not be used in the presence of asthma, gangrene, diabetes, cardiovascular disease, mechanical obstruction of the intestines or urogenital tract or any vagotonic state, and in patients receiving choline esters or depolarizing neuromuscular blocking agents.

WARNING: If excessive symptoms of salivation, emesis, urination and defecation occur, the use of ANTILIRIUM should be terminated. If excessive sweating or nausea occur, the dosage should be reduced.

Intravenous administration should be at a slow, controlled rate, no more than 1 mg. per minute (see dosage). Rapid administration can cause bradycardia, hypersalivation leading to respiratory difficulties and possibly convulsions.

An overdosage of ANTILIRIUM can cause a cholinergic crisis.

PRECAUTIONS: Because of the possibility of hypersensitivity in an occasional patient, atropine sulfate injection should always be at hand since it is an antagonist and antidote for physostigmine.

ADMINISTRATION AND DOSAGE: The usual adult dose of ANTILIRIUM is 0.5 to 2.0 mg. intramuscularly or intravenously. Intravenous administration should be at a slow, controlled rate of no more than 1 mg. per minute. It may be necessary to repeat dosages of 1 mg. to 4 mg. at intervals as life threatening signs such as arrhythmias, convulsions and deep coma recur.

IN ALL CASES OF POISONING, THE USUAL SUPPORTIVE MEASURES SHOULD BE UNDERTAKEN.

SUPPLIED: 2 ml. ampules containing:
PHYSOSTIGMINE SALICYLATE 1 mg. per ml.
Packed 12 ampules per box.

NDC 0456-1037-12

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES:

Greene, L. T.: Physostigmine treatment of anticholinergic drug depression in postoperative patients. Anesth & Analg, March-April 1971; 50-2: 222-226.

Rumack, B.: Anticholinergic poisoning: Treatment with physostigmine. Pediatrics, Sept. 1973.

Slovis, T. L., Ott, J. E., Tietelbaum, D. T., and Lipscomb, W.: Physostigmine therapy in acute tricyclic antidepressant poisoning. Clinical Toxicology, 4:451, 1971.

DRUGS AND CHEMICALS CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING:

- AMITRIPTYLINE (Elavil, Triavil, Etrafon)
- ANISOTROPINE METHYLBROMIDE
- ATROPINE
- BELLADONNA
- BENACTYZINE
- CHLORPHENIRAMINE
- CYCLOPENTOLATE
- DESIPRAMINE (Norpramin, Pertofrane)
- DICYCLOMINE
- DIPHENHYDRAMINE
- DOXEPIN (Sinequan)
- HOMATROPINE
- HYOSCINE
- HYOSCYAMUS
- IMIPRAMINE (Tofranil, Presamine)
- ISOPROPAMIDE
- MEPENZOLATE
- METHANTHELINE
- METHAPYRILENE
- NORTRIPTYLINE (Aventyl)
- PIPENZOLATE BROMIDE (Piptal)
- PROPANTHELINE
- PROTRIPTYLINE (Vivactil)
- PYRILAMINE
- SCOPOLAMINE
- STRAMONIUM
- PHENOTHIAZINES
- TRICYCLIC ANTIDEPRESSANTS (Aventyl, Elavil, Etrafon, Norpramin, Pertofrane, Presamine, Tofranil, Triavil, Vivactil)
- THIORIDAZINE (Mellaril)

O'NEAL, JONES & FELDMAN, INC.
1304 ASHBY ROAD • ST. LOUIS, MISSOURI 63132 • (314) 997-6650

CLASSIFIED ADVERTISING

ANESTHESIOLOGIST — markedly expanding academic medical center located in attractive Midwestern setting requires additional senior and junior faculty; Board certification and teaching experience necessary; salary from $45,000-$75,000 with extraordinary fringe benefit program. Inquiries with curriculum vitae to Box 5-76-B in care of I.A.R.S.

ANESTHESIOLOGIST: Board certified/eligible to join newly formed group of anesthesiologists and nurse anesthetists in New Orleans. Fee for service private practice at 650-bed general hospital and newly opened Pediatric hospital. Write or call Metropolitan Anesthesia Associates, 4520 Melpomene, New Orleans, La. 70185. (504) 822-9331.

ANESTHESIOLOGIST—to join staff in new 400+ bed university affiliated teaching hospital in large metropolitan area. Candidates must be licensed or eligible for licensure in the state of Minnesota at the time they are accepted for employment. Salary commensurate with experience. For further information contact:

Irving Greenfield, Chief of Service
Dept. of Anesthesia
Hennepin County Medical Center
5th and Portland
Minneapolis, MN 55415

FACULTY POSITIONS

Department of Anesthesiology, Charity Hospital, New Orleans, affiliated with LSU and Tulane Medical Schools, has three faculty positions open for board certified/eligible anesthesiologists at Associate-Assistant Professor, Instructor levels. Duties involve teaching, research, clinical supervision. Salaries negotiable. Send inquiries and curriculum vitae to: M. Naraghi, M.D., Director, Department of Anesthesiology, Charity Hospital, New Orleans, Louisiana 70140.

DENTAL ANESTHESIOLOGY RESIDENCY

Available to dentists who have completed no less than one year of an approved internship or residency. Stipend: $15,400 at first year level.

For further details write to: Dr. Leon Eisenbud, Chairman, Department of Dentistry, Long Island Jewish-Hillside Medical Center, New Hyde Park, New York 11040.

MARYLAND: Positions on the Anesthesia Staff at Baltimore City Hospitals. Excellent fringe benefits and salary. Residency fully integrated with the Johns Hopkins Medical School program. Send CV to Peter Chodoff, M.D., Anes-in-Chief, Baltimore City Hospitals, 4940 Eastern Ave., Baltimore, Maryland 21224.

PEDIATRIC ANESTHESIOLOGY RESIDENCY

Childrens Hospital of Los Angeles

Three-phase program: Clinical, Academic, Investigative, emphasizing practical aspects of anesthesiology related to infants and children.

AMA approval for third-year residency. Positions available from two months to one year.

Apply: George B. Lewis, Jr., M.D.
Head, Division of Anesthesiology
Childrens Hospital of Los Angeles
4650 Sunset Boulevard
Los Angeles, California 90054
Phone (213) 660-2450, Ext. 2262

NEBRASKA Opportunity for Anesthesiologist in 450-bed acute care, teaching hospital affiliated with two medical schools; must be board certified or eligible, salary commensurate with education and experience. An equal opportunity employer. Contact J. J. Matoole, M.D., Chief of Staff, Veterans Administration Hospital, 4101 Woolworth Avenue, Omaha, Nebraska 68105. (402) 346-8800, Ext. 442.

5th ANESTHESIOLOGIST—Board certified/eligible. To join hospital based group with new OR in modern 250-bed community hospital. Excellent opportunity. Send CV to Raymond E. Bradley, M.D., Chief Anesthesiologist, The Griffin Hospital, 130 Division St., Derby, Conn. 06418. Equal opportunity employer.

DIRECTOR OF PULMONOLOGY

Responsibility will include developing, supervising and directing acute and chronic pulmonary services for 376-bed acute hospital and 230-bed long term care hospital. Will assist to develop new services to improve pulmonology accessibility to our patients and to physicians and patients of contracting health care institutions in the area. Position requires a Board Certified Pulmonologist. Please direct inquiries to: Dr. John Hoesing, Chairman, Pulmonology Director Search Committee,

Nebraska Methodist Hospital
8300 Dodge Street
Omaha, Nebraska 68114
(402) 397-3000

An Equal Opportunity Employer

ACADEMIC ANESTHESIOLOGIST

Top academic salaries in country, rank commensurate with vitae, any experience level considered, must be A.B.A. certified, type of assignment dependent on interest but especially seeking cardiovascular and O.B. experience, research opportunities also available. Send Vitae, date of availability, and list three references. Contact Box 7-76-A, c/o I.A.R.S.

Rates for classified advertising are $3.00 per line, minimum 5 lines. Box number ads $3.50 per line. Classified Display rates on request. Copy deadline 6 weeks prior to publication. Do not submit payment with order; invoices will be sent for payment prior to publication. Ad copy, subject to acceptance by publisher, should be mailed to: Anesthesia and Analgesia . . . Current Researches, 3645 Warrensville Center Rd., Cleveland, Ohio 44122.

The local that gives you the longest anesthesia gives your patient longer postoperative analgesia.

Marcaine® hydrochloride (brand of bupivacaine hydrochloride)—available with or without epinephrine—is the local anesthetic that provides the longest duration of action among commonly used local anesthetics. Which minimizes the problems of "continuous" technique or repeat doses.

Marcaine also provides longer postoperative analgesia. Which reduces the need for postoperative narcotics.

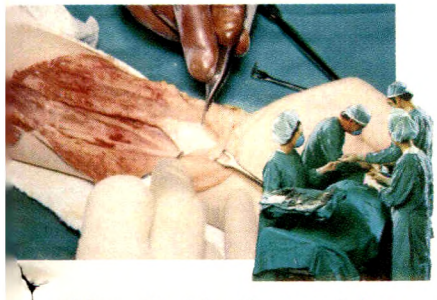
And in data in over 3,000 patients, Marcaine was reported to have excellent or satisfactory results in more than 96% of cases.

Extended anesthesia for the surgeon

In regional blocks, Marcaine, with or without epinephrine, usually provides anesthesia at least 1½ to 2 times longer than lidocaine or mepivacaine. And approximately 20% longer than tetracaine.

In fact, anesthesia may extend up to 9 hours for peridural block and up to 12 hours for peripheral nerve block. This has been established in several thousand surgical and obstetrical patients.[1-4]

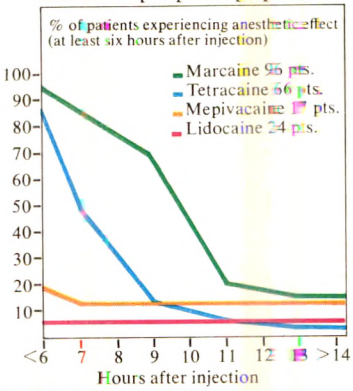
In fact, a single Marcaine epidural injection, with or without epinephrine, may be enough for up to 3½[4] or more[5] hours of anesthesia for surgery, and often provides analgesia that carries over into the recovery room and beyond. When necessary, doses may be repeated up to once every three hours. Caution is advised in administration of repeat doses to patients with severe liver disease. Until further experience is gained, total daily dose of



400 mg. should not be exceeded nor is administration to children under 12 recommended. Also see epinephrine warnings and precautions statements on next page.

This longer anesthetic action can minimize problems of "continuous" technique or repeat doses. Thus, there is the further advantage of a reduced likelihood of introducing infection since injections are less frequent.[6]

Chart I
Duration of anesthesia
Percentage of patients experiencing anesthetic effect—
Comparison of Marcaine with epinephrine and other local anesthetic/epinephrine preparations*



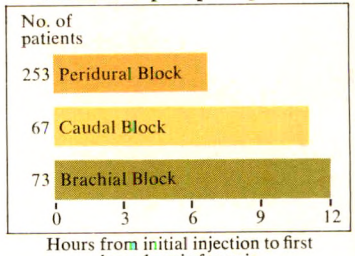
*Equipotent doses used for bilateral, simultaneous blocks of sciatic/femoral, intercostal or brachial/axillary nerves. Adapted from Moore, D. C.: Data in the files of the Sterling-Winthrop Research Institute.

Extended postoperative analgesia for the patient

Marcaine, with or without epinephrine, gives your patient more—considerably more—postanesthetic analgesia than other local anesthetics in various types of nerve block.[3,4,7,8] An analgesia that persists after the return of motor function and even cutaneous sensation.[7] As a result, you may be able to defer[1,5] and sometimes even eliminate,[5] postoperative narcotics. Chart II illustrates the average duration of time between the initial Marcaine injection and the need for postop analgesics. Many of the 67 patients given Marcaine, with or without epinephrine, caudally for rectal surgery did not complain of pain for 11 hours or longer following induction.

In another group of 40 patients[8] given Marcaine or mepivacaine, both with epinephrine, locally for tonsillectomy, Marcaine pain relief lasted 3 to 5 times longer than that provided by mepivacaine. And in a study[1] of 65 patients given 0.5% Marcaine with epinephrine caudally for rectal or other perineal surgery, complete sensation returned in a mean of 8½ hours for the average patient. And the majority of these patients did not require a narcotic for an additional 1 to 3 hours.

Chart II
Duration of time between injection of Marcaine, with or without epinephrine, and need for postop analgesics†



†Average—exclusion of extremes and failures. Adapted from Lund, P.C., *et al.*: *Anesth. Analg.* 49:103, Jan.-Feb. 1970.

Excellent clinical acceptance

Marcaine, with or without epinephrine, was administered to 3,112 patients for various types of local anesthesia.[9] Of these patients, only 2 experienced a systemic reaction. Although Marcaine has a very wide safety margin, adverse reactions characteristic of those associated with other amide local anesthetics may occur.

Marcaine is indicated for most anesthetic blocks; however, until further clinical experience is gained, paracervical block is not recommended.

See important product information concerning warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations on next page.

Extends the limits of time in anesthesia[1-4]
Extends the limits of time in postoperative analgesia[3,4,7,8]

Marcaine® hydrochloride

Brand of
bupivacaine hydrochloride

with or without epinephrine 1:200,000

Winthrop

MARCAINE® Hydrochloride
Brand of **bupivacaine hydrochloride**

Indications: Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

Contraindication: Marcaine is contraindicated in patients with known hypersensitivity to it.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. Reproduction studies have been performed in rats and rabbits and there is no evidence of harm to the animal fetus. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions: The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Adverse Reactions: Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings).

Allergic reactions, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

References: 1. Moore, D. C., Bridenbaugh, L. D., Bridenbaugh, P. O., *et al.*: Bupivacaine, a review of 2,077 cases, *J.A.M.A. 214*:713, Oct. 26, 1970. **2.** Moore, D. C., Bridenbaugh, L. D., Bridenbaugh, P. O., *et al.*: Bupivacaine for peripheral nerve block: a comparison with mepivacaine, lidocaine and tetracaine, *Anesthesiology 32*:460, May 1970. **3.** Hollman, A.: Axillary plexus block: a double-blind study of 59 cases using mepivacaine and LAC-43, *Acta Anaesthesiol. Scand., Suppl. 21*:53, 1966. **4.** Bromage, P. R.: A comparison of bupivacaine and tetracaine in epidural anesthesia for surgery, *Can. Anaesth. Soc. J. 16*:37, Jan. 1969. **5.** Lund, P. C., Cwik, J. C., and Vallesteros, F.: Bupivacaine—a new long-acting local anesthetic agent, a preliminary clinical and laboratory report, *Anesth. Analg. 49*:103, Jan.-Feb. 1970. **6.** Wise, G. F.: Guest Discussions, *Anesth. Analg. 49*:113, Jan.-Feb. 1970. **7.** Moore, D. C.: Data in the files of the Sterling-Winthrop Research Institute. **8.** Puento-Egido, J. J., Dudeck, J., and Nolte, H.: The clinical use of the local anesthetic agent Marcaine (Carbostesin®), *Anaesthesist 16*:224, August 1967. **9.** Data in the files of the Sterling-Winthrop Research Institute. (1664MB)

Winthrop

Winthrop Laboratories, New York, N.Y. 10016

FORMULA

PRODUCT IDENTIFICATION			MULTIPLE DOSE VIAL						SINGLE DOSE AMPUL				
Marcaine HCl (brand of bupivacaine HCl)		Epinephrine* (as bitartrate)	Methylparaben	Sodium Bisulfite	Thioglycerol	Ascorbic Acid	60% Sod. Lactate	Edetate Calcium Disodium	Sodium Bisulfite	Thioglycerol	Ascorbic Acid	60% Sod. Lactate	Edetate Calcium Disodium
%	mg./ml.	Dilution	mg./ml.	mg./ml.	ml./ml.	mg./ml.	ml./ml.	mg./ml.	mg./ml.	ml./ml	mg./ml.	ml./ml.	mg./ml.
0.25	2.5	—	1	—	—	—	—	—	—	—	—	—	—
0.25	2.5	1:200,000	1	0.5	.001	2	.0017	0.1	.5	.001	2	.0017	0.1
0.5	5.0	—	1	—	—	—	—	—	—	—	—	—	—
0.5	5.0	1:200,000	1	0.5	.001	2	.0017	0.1	.5	.001	2	.0017	0.1
0.75	7.5	—							—	—	—	—	—
0.75	7.5	1:200,000	Not Available in Vials						.5	.001	2	.0017	0.1

Note: The pH of these solutions is adjusted with sodium hydroxide or hydrochloric acid. Sodium chloride has been added to make each solution isotonic.

*Solutions of Marcaine that contain epinephrine should not be autoclaved.

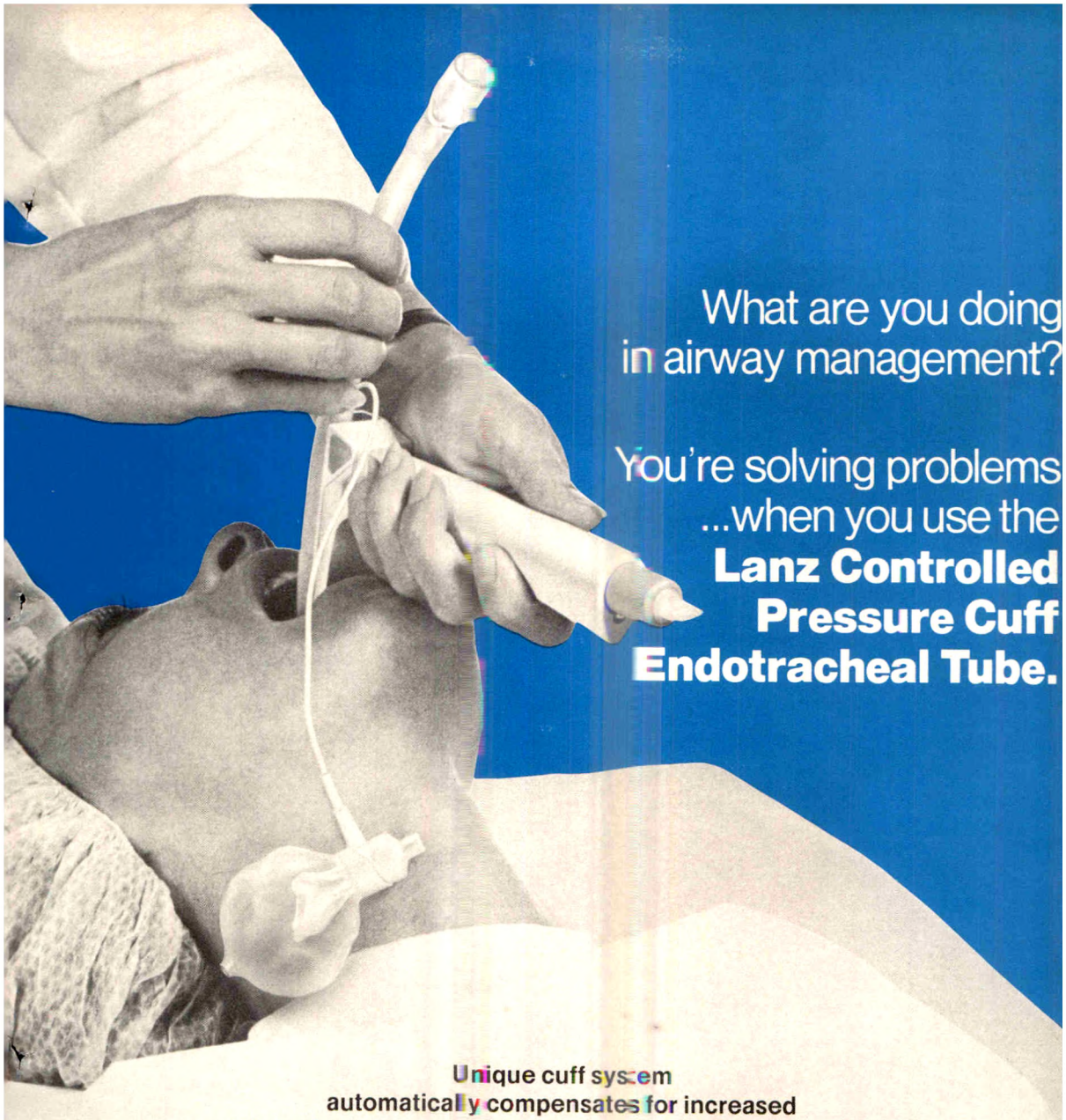
Federal law prohibits dispensing without a prescription.

Extends the limits of time in anesthesia[1-4]
Extends the limits of time in postoperative analgesia[3,4,7,8]

Marcaine® hydrochloride

Brand of
bupivacaine hydrochloride

with or without epinephrine 1:200,000



What are you doing in airway management?

You're solving problems ...when you use the **Lanz Controlled Pressure Cuff Endotracheal Tube.**

Unique cuff system automatically compensates for increased volume/pressure caused by diffusion of N_2O or O_2 into cuff.

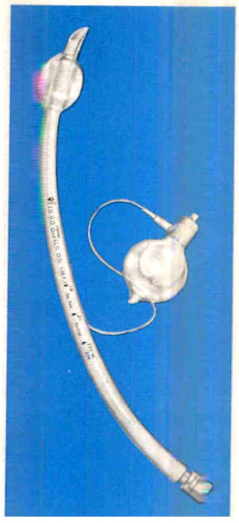
Long-term airway management is a problem. There's always the hazard of tracheal scarring and stenosis...accidental over-inflation. And so on.

Now with the Lanz Controlled-Pressure Cuff Endotracheal Tube, you can help solve your long-term intubation problems.

Dangers of Tracheal Damage Minimized.

The Lanz Endotracheal Tube is unique. It is a controlled-pressure cuff system containing an automatic, pressure regulating valve with an external, pressure-control balloon. This system is designed to eliminate excessive pressure on the tracheal wall due to over-inflation of the cuff. It's also designed to *automatically compensate* for increased volume and pressure caused by diffusion of N_2O or O_2 into the cuff.

When used in the intubation period before tracheostomy, it helps assure protection of the trachea throughout the entire period of airway management.



Patient Safety and Comfort

The Lanz Endotracheal Tube permits quick and easy intubation. The tube will flex, but not kink. It is available with either Murphy or Magill tips.

And it's available now—packaged sterile, and ready to use.

Help solve your long-term airway problems now with the Lanz Disposable Controlled-Pressure Cuff Endotracheal Tube. Write today for complete information, or call your Extracorporeal Representative.

extracorporeal

Extracorporeal Medical Specialties, Inc.
Royal & Ross Roads · King of Prussia Pa 19406 U.S.A. 215-337-2400

In Europe, write:
Extracorporeal S.A., 253 Avenue Winston Churchill, B-1180 Brussels, Belgium

INTRODUCING

the PSI 5000 Recorder

MEASURES & RECORDS

ECG • PULSE •
VITAL PRESSURES

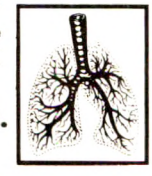
- ARTERIAL
- VENOUS
- INTERCRANIAL
- PULMONARY WEDGE

WHEN VERSATILITY COUNTS

BATTERY OPERATION, VARIABLE AMPLITUDES
VARIABLE SPEEDS AND TREND - 2.5 to 50 mm/Sec.

Whenever precise permanent copies are essential.

The PSI 5000 Recorder is a portable, battery operated, self-contained unit for use in most heart, lung, and blood pressure measurements. The PSI 5000 meets AHA specifications for electrocardiography, assuring superior performance in any application requiring high frequency response. The pen stylus is held in a stress-free mount on a titanium arm to provide exceptional life. It is capable of sustaining up to 1000 G's acceleration. A fully charged battery will provide up to four hours continuous operation.



Pulmonary Specialties, Inc.

231 COMMERCE DRIVE, LARGO, FLORIDA 33540 • TELEPHONE (813) 585-4772

PRECISE, ECONOMICAL, SAFE . . .

RALS POWER UNIT

. . . INSTANT ATOMIZATION FOR FAST TOPICAL ANESTHESIA

Fast, measured topical anesthesia is ready at your finger tips in a Rals Power Unit. Forget about pumping bulbs, uneven atomization, and limited spraying duration. The Rals Power Unit uses a non-toxic propellant, dichlorodifluoromethane (freon) to activate standard DeVilbiss Atomizers No's. 151, 152 and 163. Instantly, a fine mistlike spray is produced. A graduated solution vial is available for measuring the amount of solution administered.

The Rals Power Unit has been proven effective in cocainization prior to endotracheal intubation, endoscopic instrumentation, laryngotracheal insufflation, and in a variety of nose and throat procedures.

Rals Power Unit #168 are supplied six to a box with adaptor top and metal base. Illustration shows #152 atomizer. All styles in stock.

WRITE OR PHONE FOR LITERATURE, PRICE LIST.

RALS LABORATORIES DIVISION
SCHUEMANN Laboratories, Inc.
480 WEST AURORA ROAD • NORTHFIELD, OHIO 44067

SL-45

A mainstay of modern anesthesia

- As an adjunct to general anesthesia
- As a supplement to regional anesthesia
- Used without a general anesthetic in certain diagnostic procedures

INNOVAR® injection is available for use only upon direction of a physician.

Special educational material available

A Programmed Instruction Manual on the chemistry, pharmacology and clinical applications of INNOVAR injection and its components is available from McNeil Laboratories. For further information, please write: Product Director, INNOVAR injection, McNeil Laboratories, Inc., Fort Washington, Pa. 19034.

© McN 1975

For prescribing information including Contraindications, Warnings, Precautions and Adverse Reactions, please turn page.

Innovar® injection

The two components of INNOVAR® injection, fentanyl and droperidol, have different pharmacologic actions. Before administering INNOVAR injection, the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action.

DESCRIPTION

Each cc. contains (in a 1:50 ratio):

Fentanyl ..... 0.05 mg.
as the citrate

Warning: May be habit forming

Droperidol ..... 2.5 mg.

Lactic acid for adjustment of pH to 3.5± 0.3

FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY

Protect from Light

ACTIONS INNOVAR injection is a combination drug containing a narcotic analgesic, fentanyl, and a neuroleptic (major tranquilizer), droperidol. The combined effect, sometimes referred to as neuroleptanalgesia, is characterized by general quiescence, reduced motor activity, and profound analgesia; complete loss of consciousness usually does not occur from use of INNOVAR injection alone. The incidence of early postoperative pain and emesis may be reduced.

A. Fentanyl is a narcotic analgesic with actions qualitatively similar to those of morphine and meperidine. Fentanyl in a dose of 0.1 mg. (2.0 cc.) is approximately equivalent in analgesic activity to 10 mg. of morphine or 75 mg. of meperidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. Fentanyl appears to have less emetic activity than other narcotic analgesics. Histamine assays, and skin wheal testing in man, as well as *in vivo* testing in dogs indicate that histamine release rarely occurs with fentanyl.

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. It may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia, and bronchoconstriction.

The onset of action of fentanyl is almost immediate when the drug is given intravenously; however, maximal analgesic and respiratory depressant effect may not be noted for several minutes. The average duration of action of the analgesic effect is 30 to 60 minutes. Following intramuscular administration, the onset of action is from seven to eight minutes, and the duration of action is from one to two hours. Although the duration of the respiratory depressant effect is unknown, as with other narcotic analgesics, it may be considerably longer than the analgesic effect.

B. Droperidol produces marked tranquilization and sedation. It also produces an antiemetic effect as evidenced by the antagonism of apomorphine in dogs. It potentiates other CNS depressants. It also produces mild alpha adrenergic blockade, peripheral vascular dilatation and reduction of the pressor effect of epinephrine. Droperidol can produce hypotension and decreased peripheral vascular resistance. It may decrease pulmonary arterial pressure (particularly if it is abnormally high). It may reduce the incidence of epinephrine-induced arrhythmias but it does not prevent other cardiac arrhythmias. The onset of action is from three to ten minutes following intravenous or intramuscular administration. The full effect, however, may not be apparent for 30 minutes. The duration of the sedative and tranquilizing effects generally is two to four hours. Alteration of consciousness may persist as long as 12 hours. This is in contrast to the much shorter duration of action of fentanyl.

INDICATIONS INNOVAR injection is indicated to produce tranquilization and analgesia for surgical and diagnostic procedures. It may be used as an anesthetic premedication, for the induction of anesthesia, and as an adjunct in the maintenance of general and regional anesthesia. If the supplementation of analgesia is necessary, SUBLIMAZE® (fentanyl) injection alone rather than the combination drug INNOVAR injection should usually be used.

CONTRAINDICATIONS INNOVAR injection should not be used in patients who are hypersensitive to either component.

WARNINGS PATIENTS WHO HAVE RECEIVED *INNOVAR* INJECTION SHOULD BE UNDER APPROPRIATE SURVEILLANCE.

RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INNOVAR injection, the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses, as low as 1/4 to 1/3 those usually recommended.

INNOVAR injection may cause muscle rigidity, particularly involving the muscles of respiration. This effect is due to the fentanyl component and is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs it is managed by the use of assisted or controlled respiration and by a neuromuscular blocking drug, if necessary.

FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD ALSO BE AVAILABLE.

Drug Dependence: *Fentanyl, the narcotic analgesic component, can produce drug dependence of the morphine type and therefore has the potential for being abused.*

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl, in this regard, has not been established, the use of INNOVAR injection or SUBLIMAZE fentanyl in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure: INNOVAR injection should be used with caution in patients who may be particularly susceptible to respiratory depression such as comatose patients who may have a head injury or brain tumor. In addition, these drugs may obscure the clinical course of patients with head injury.

Usage in Children: The safety of INNOVAR injection in children two years of age or younger has not been established.

Usage in Pregnancy: The safe use of INNOVAR injection has not been established with respect to possible adverse effects upon fetal development.

Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS *The initial dose of INNOVAR injection should be appropriately reduced in elderly, debilitated and other poor risk patients. The effect of the initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves, and can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms (see Actions) fentanyl and droperidol also depress respiration and blood pressure. Therefore, when INNOVAR injection is used to supplement these forms of anesthesia, the anesthetist must be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

The droperidol component of INNOVAR injection may decrease pulmonary arterial pressure. This fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient.

Vital signs should be monitored routinely.

INNOVAR injection, and SUBLIMAZE fentanyl, should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised ventilation. In such patients narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia this can be managed by assisted or controlled respiration. Postoperatively respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists (levallorphan, nalorphine, and naloxone); consult individual prescribing information before using.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INNOVAR injection. When patients have received such drugs, the dose of INNOVAR injection required will be less than usual. Likewise, following the administration of INNOVAR injection the dose of other CNS depressant drugs should be reduced.

INNOVAR injection should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in the moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus these other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INNOVAR injection due to the alpha-adrenergic blocking action of droperidol.

The fentanyl component may produce bradycardia, which may be treated with atropine; however, INNOVAR injection should be used with caution in patients with cardiac bradyarrhythmias.

When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

ADVERSE REACTIONS The most common serious adverse reactions reported to occur with INNOVAR injection are respiratory depression, apnea, muscular rigidity, and hypotension; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, twitching, blurred vision, hyperactivity on induction, laryngospasm, transient hypertension, nausea and emesis, diaphoresis, emergence delirium and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).

Postoperative drowsiness is also frequently reported.

OVERDOSAGE ***Manifestations:*** The manifestations of INNOVAR injection overdosage are an extension of its pharmacologic actions.

Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered. A specific narcotic antagonist such as nalorphine, levallorphan or naloxone should be available for use as indicated to manage respiratory depression caused by the narcotic component fentanyl. This does not preclude the use of more immediate countermeasures. Consult the package inserts for the individual narcotic antagonists for details about use.

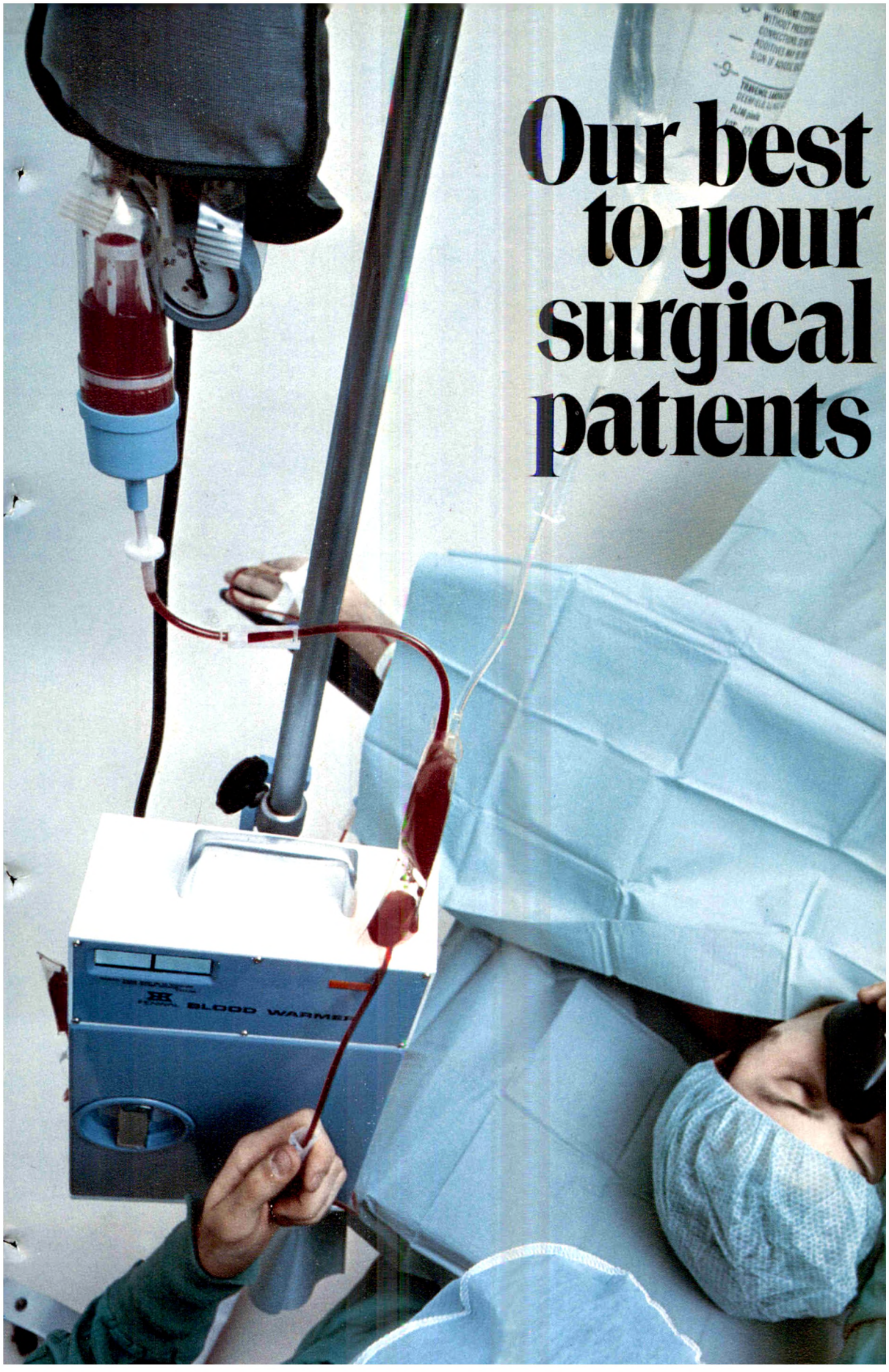
HOW SUPPLIED INNOVAR® injection is supplied in 2 cc. (**NDC** 0045-0280-20) and 5 cc. (**NDC** 0045-0280-50) ampuls, in packages of 10.

IMPORTANT: Complete dosage information is available in insert which accompanies each package (or on request). The drug is available only upon direction of a physician.

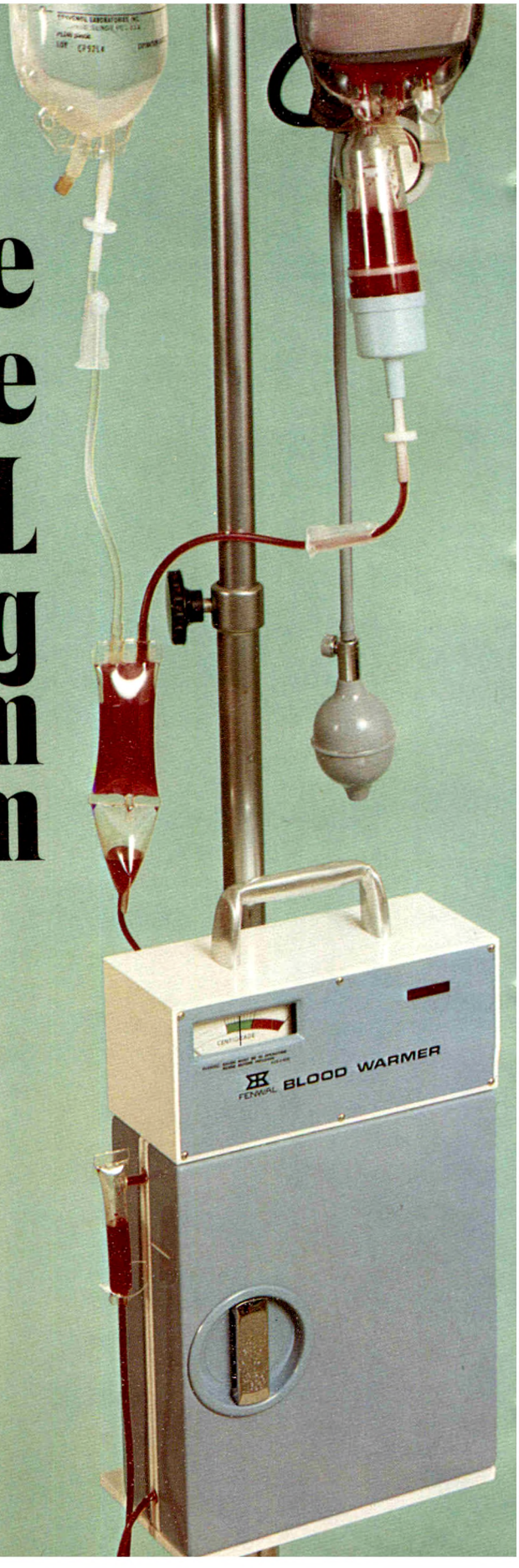
U.S. Patent No. 3,141,823

9/74

McNEIL **McNeil Laboratories, Inc.**
Fort Washington, Pa. 19034


Our best
to your
surgical
patients

The complete FENWAL operating room system



The Fenwal Dry Heat Blood Warmer is designed for use during single or multiple transfusions when precise regulation of blood temperature and flow rate is indicated. It utilizes a disposable plastic blood-warming pathway.

Fenwal Recipient Sets are available to accommodate your infusion requirements. The Single Lead Set is to be used for the intravenous administration of one unit of whole blood, red cells or plasma. The "Y" Recipient Set is designed to permit dual hookups for simultaneous administration of blood and/or solutions. The Triple Lead Set may be employed in multiple infusion procedures, i.e., blood, solutions, blood components and medication.

The Fenwal Microaggregate Blood Filter is designed to remove microaggregates down to 20 microns in size during intravenous administration of stored whole blood or red cells.

Fenwal Pressure Infusors provide an efficient non-air-dependent method for the rapid infusion of whole blood or red cells.

The Fenwal TYPENEX™ Blood Recipient Identification System ties together the identity of the transfusion candidate, his cross-match request form, blood sample and up to 10 cross-matched units of blood.

The Fenwal Venous Pressure Manometer Set is a disposable, preassembled unit that permits continuous monitoring of the patient's venous pressure while performing one simple hookup.

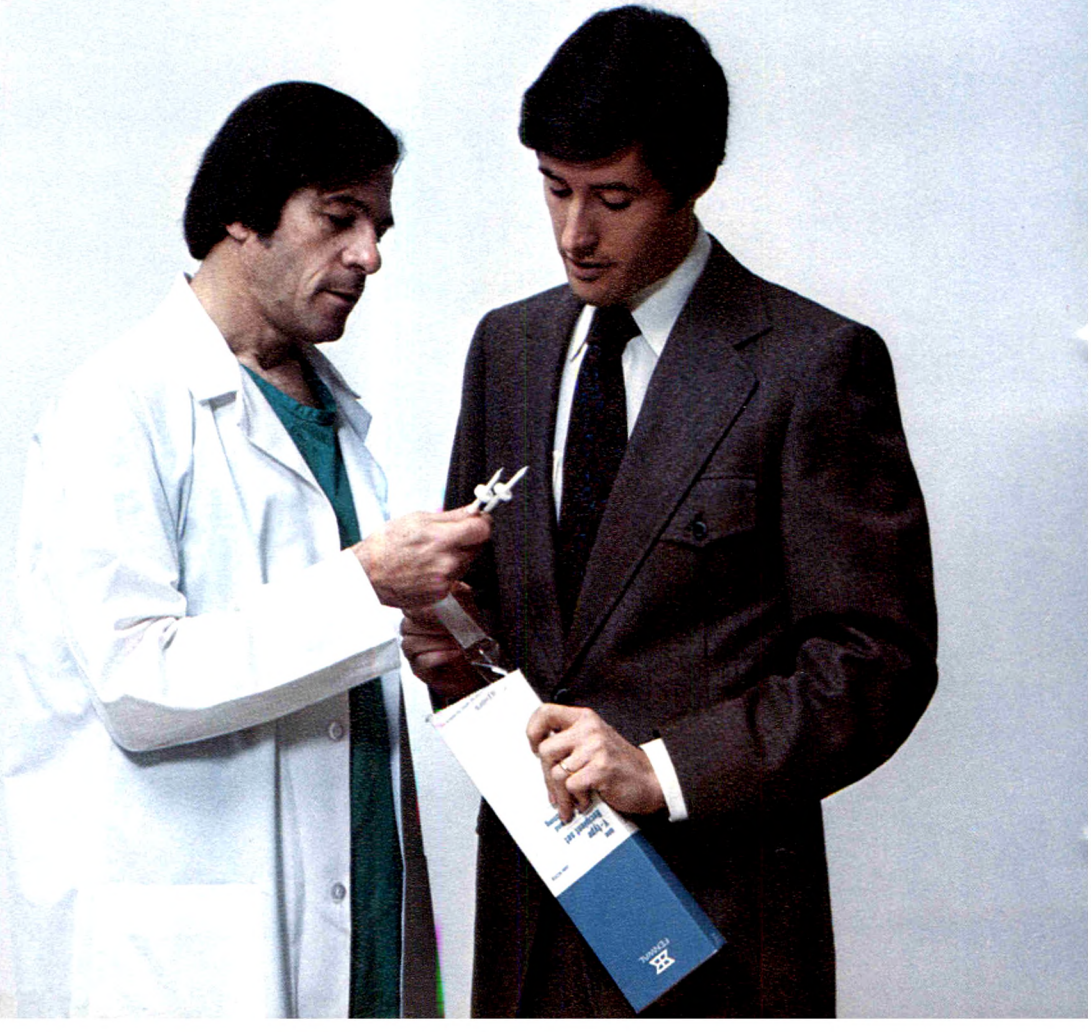
The Fenwal Platelet Recipient Set is designed specifically for the infusion of fresh blood and pool platelet concentrates.

Our best to you

Fenwal Laboratories has long been identified with innovation in modern blood handling systems. Our knowledge and experience in developing and providing sophisticated blood processing systems have earned a reputation for excellence. Thoroughly researched and tested to meet the demands of the medical profession, you can expect the same quality in Fenwal operating room devices that helped achieve our recognition with the nation's blood banks.

The Fenwal Specialist in your hospital can provide you and the other members of the operating team with completely detailed information on all of our products. Intensive training makes him fully qualified to answer your most involved questions regarding up-to-date blood transfusion procedure. Be sure to see your Fenwal Specialist the next time he visits your department.

FENWAL LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois, U.S.A. 60015.



U.S. Patent applied for.

Ref: Corneal Injuries During General Anesthesia, Anesthesia and Analgesia, Vol. 54, No. 4, July-August, 1975

Protect patients' eyes with OPTI-GARD™

Why tape eyelids shut and risk skin abrasion, loss of eyelashes, and contact dermatitis? Dupaco Opti-Gard,™ for use during general anesthesia and post-op recovery, effectively and comfortably helps prevent corneal abrasion, lacerations, and scleral hemorrhage. Opti-Gard™ also protects against blood, fluid, or other foreign materials entering the eyes . . . a vital consideration in ENT, head, or neck surgery. Sterile packaged and boxed in convenient dispenser, Opti-Gard™ clear plastic protective covers come with self adhesive foam cushion. **Send for free sample.**

DUPACO
INCORPORATED
P.O. Box 98, San Marcos, Ca. 92069

FOR THE ATTENTION OF

PROGRAM DIRECTORS and STUDENTS IN MEDICAL, DENTAL, OSTEOPATHIC AND NURSE ANESTHESIA TRAINING PROGRAMS

Please clip and mail this to:

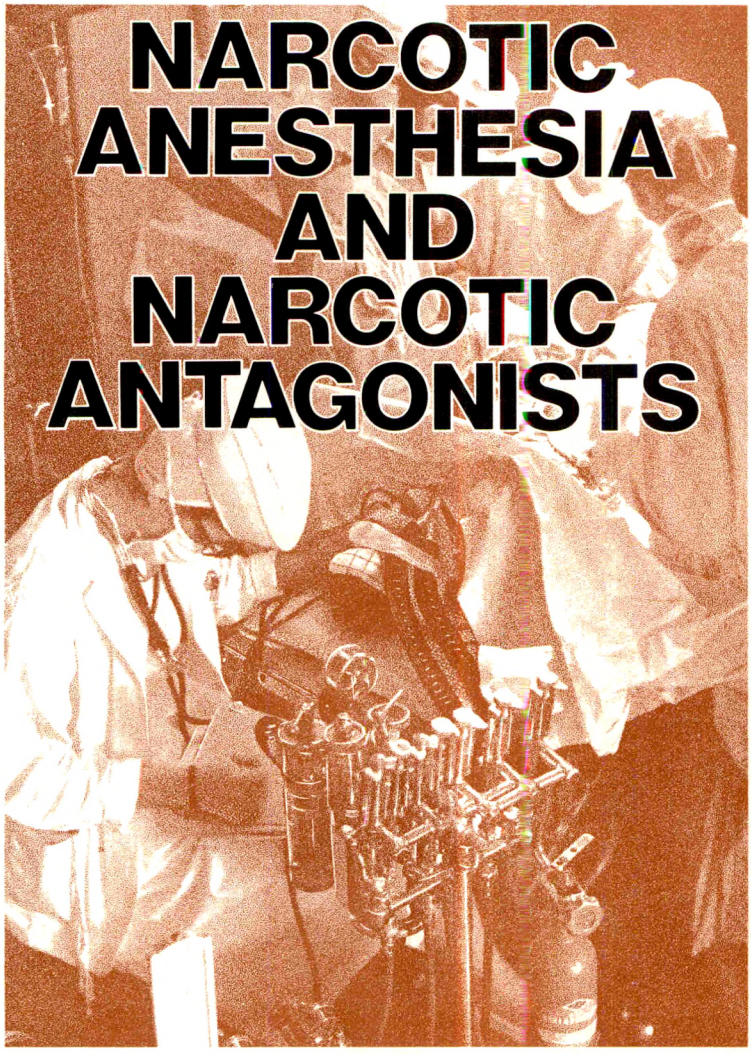
International Anesthesia Research Society
3645 Warrensville Center Rd., Cleveland, Ohio 44122

☐ I am a Program Director in an accredited anesthesia or anesthesia related (physician assistant, inhalation therapy) training program and would like to have _____ Educational Membership applications for students enrolled in my program.

☐ I am a student enrolled in an accredited anesthesia or anesthesia related training program. Please send me application for Educational Membership which includes a two-year subscription to ANESTHESIA and ANALGESIA . . . Current Researches for $25.

(NAME - PLEASE PRINT) (INSTITUTION)

(MAIL ADDRESS) (CITY, STATE AND ZIP)



NARCOTIC ANESTHESIA

- Despite many advantages, the use of opioids to supplement nitrous oxide anesthesia may be associated with significant postoperative depression.

NARCAN® (naloxone HCl)

- Narcan® in sufficient doses will antagonize opioid effects, including all degrees of respiratory depression and analgesia.
- The degree of narcotic antagonism exhibited by NARCAN® is dose dependent.

A recent study of surgical patients receiving narcotic-nitrous oxide anesthesia was undertaken to determine whether careful titration of naloxone would reverse post-operative narcotic depression and maintain a subjective level of analgesia.[1]

THE OBJECTIVES:

- Restore consciousness
- Reverse narcotic-induced respiratory depression as evidenced by $PaCO_2$
- Maintain *subjective* analgesia

THE METHOD:

- 12 unpremedicated patients received INNOVAR® (fentanyl/droperidol) 5-10 ml I.V. followed by thiopental for induction. Anesthesia was maintained with N_2O-O_2. Increments of 0.1 mg *fentanyl* were given I.V. every 10 minutes during surgery.

Following the procedure, naloxone (0.1 mg/ml) was given in 0.1 mg I.V. increments at 1 minute intervals until the patient was awake, lucid and had adequate tidal and minute volumes. Additional naloxone

1. Heisterkamp DV, Cohen PJ: *Anesth Analg* (Cleve) 53:12-18, Jan-Feb 1974.

NARCAN® is an Endo registered U.S. trademark; U.S. Pat. 3,254,088.

was given I.V. as needed in the first 6 patients; a second group of 6 patients received supplemental naloxone I.M. 30 minutes after the initial I.V. dose.

- 11 patients received 10 mg *morphine* I.M., as well as secobarbital and atropine, 1½ hours preoperatively. Anesthesia was induced by 30 mg morphine given slowly I.V. followed by thiopental and was maintained by N_2O-O_2. Additional morphine was given in divided increments to total 1 mg/kg in the first hour. Further morphine was given as needed. For initial narcotic reversal, naloxone was given as above except at 2 minute intervals. Supplemental naloxone was given I.M. 30 minutes later.

THE RESULTS (fentanyl group):

- When fentanyl was used as the sole narcotic supplement during anesthesia, an I.M. dose of naloxone equal to half the I.V. reversal dose and given ½ hour later provided adequate narcotic reversal.

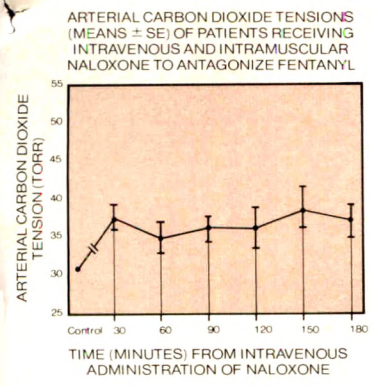


Fig. 1. Control and postoperative $PaCO_2$ in 6 patients receiving I.V. and I.M. naloxone following fentanyl.

THE RESULTS (morphine group):

- "After other narcotics, such as morphine, an I.M. dose of naloxone equal to the I.V. dose appears appropriate."

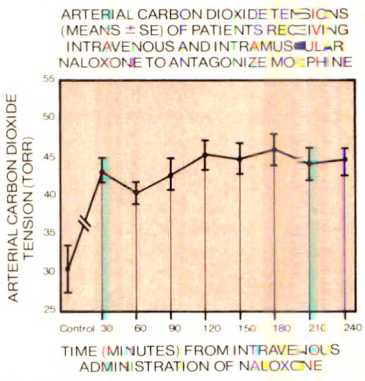


Fig. 2. Control and postoperative $PaCO_2$ in 11 patients receiving I.V. and I.M. naloxone following morphine.

THE CONCLUSIONS:

- "Naloxone provides fast, potent, and reliable antagonism to narcotic-induced respiratory depression."
- "By careful titration, this antagonism can be achieved while acceptable analgesia is maintained."
- "Both morphine and fentanyl groups had adequate analgesia, with only 2 patients [of total 21] requiring pain medication in the recovery room."

- **reverses all degrees of narcotic-induced respiratory depression**
- **does not cause narcotic-like effects**
- **does not augment non-narcotic depression**
- **acts rapidly—generally within 2 minutes following I.V. use and slightly less rapidly when given I.M.**
- **does not lead to tolerance**
- **does not produce psychotomimetic effects or pupillary constriction**
- **can be repeated if initial dose doesn't produce desired degree of narcotic reversal and improvement in respiratory function**
- **following satisfactory response patient should be observed closely and given repeat doses, if necessary, since the duration of action of some narcotics may exceed that of NARCAN®**

Please see next page for complete prescribing information.

Endo Laboratories, Inc.
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530
DUPONT

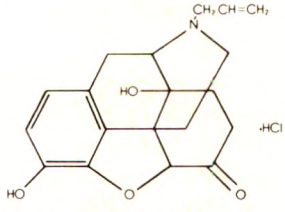
·restored consciousness
·reversed narcotic-induced respiratory depression
·maintained subjective analgesia

NARCAN®
(naloxone HCl)

can reverse narcotic-induced respiratory depression while maintaining subjective analgesia

NARCAN® (naloxone HCl)

DESCRIPTION NARCAN® (naloxone hydrochloride), a narcotic antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



NALOXONE HYDROCHLORIDE
(N-allyl-nor-oxymorphone HCl)

Naloxone hydrochloride occurs as slightly off-white crystals, and is soluble in water, slightly soluble in alcohol and practically insoluble in ether.

NARCAN® (naloxone hydrochloride) Injection is available in two concentrations, 0.02 mg and 0.4 mg of naloxone hydrochloride per ml. Each ml of either strength contains 8.6 mg of sodium chloride; and 2.0 mg of methylparaben and propylparaben as preservatives in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

ACTIONS NARCAN® (naloxone hydrochloride) is an essentially pure narcotic antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists; NARCAN® (naloxone hydrochloride) does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists it exhibits essentially no pharmacologic activity.

In the presence of physical dependence on narcotics NARCAN® (naloxone hydrochloride) will produce withdrawal symptoms; it has not been shown to produce tolerance nor to cause physical or psychological dependence.

When NARCAN® (naloxone hydrochloride) is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of NARCAN® (naloxone hydrochloride). Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of NARCAN® (naloxone hydrochloride), however, will also be dependent upon the amount, type and route of administration of the narcotic being antagonized.

INDICATIONS NARCAN® (naloxone hydrochloride) is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by natural and synthetic narcotics, propoxyphene and the narcotic-antagonist analgesic pentazocine.
NARCAN® (naloxone hydrochloride) is also indicated for the diagnosis of suspected acute opiate overdosage.

CONTRAINDICATIONS NARCAN® (naloxone hydrochloride) is contraindicated in patients known to be hypersensitive to it.

WARNINGS NARCAN® (naloxone hydrochloride) should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN® (naloxone hydrochloride) should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride).

NARCAN® (naloxone hydrochloride) is not effective against respiratory depression due to non-opioid drugs.

Usage in Pregnancy Safe use of NARCAN® (naloxone hydrochloride) during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or other embryotoxic effects (See ANIMAL PHARMACOLOGY AND TOXICOLOGY). However, NARCAN® (naloxone hydrochloride) should be administered to pregnant patients only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS In addition to NARCAN® (naloxone hydrochloride), other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

In an isolated report two patients with pre-existing ventricular irritability requiring lidocaine, and either isoproterenol or epinephrine for hypotension following cardiopulmonary bypass procedures, developed ventricular tachycardia or fibrillation when given NARCAN® (naloxone hydrochloride) I.V. at 9 and 14 hours, respectively, postoperatively for persistent unresponsiveness. Although a direct cause and effect relationship has not been established, NARCAN® (naloxone hydrochloride) should be used with caution in patients with cardiac irritability.

ADVERSE REACTIONS In rare instances nausea and vomiting have been reported in postoperative patients receiving NARCAN® (naloxone hydrochloride) in doses higher than that recommended; a cause and effect relationship has not been established.

DOSAGE AND ADMINISTRATION NARCAN® (naloxone hydrochloride) may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride) the patient should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary.

USAGE IN ADULTS Narcotic Overdose—Known or Suspected The usual initial adult dose is 0.4 mg (1 ml) NARCAN® (naloxone hydrochloride) administered I.V., I.M. or S.C. If the desired degree of counteraction and improvement in respiratory function is not obtained immediately following I.V. administration, it may be repeated intravenously at 2 to 3 minute intervals. Failure to obtain significant improvement after 2 or 3 doses suggests that the condition may be due partly or completely to other disease processes or non-opioid drugs.

Post Operative Narcotic Depression For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN® (naloxone hydrochloride) are usually sufficient. The dose of NARCAN® (naloxone hydrochloride) should be titrated according to the patient's response. Excessive dosage of NARCAN® (naloxone hydrochloride) may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or tachycardia.

For the initial reversal of respiratory depression, NARCAN® (naloxone hydrochloride) should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal i.e., adequate ventilation and alertness without significant pain or discomfort.

Repeat doses of NARCAN® (naloxone hydrochloride) may be required within one to two hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

USAGE IN CHILDREN Narcotic Overdose—Known or Suspected The usual initial child dose is 0.01 mg/kg body weight given I.V., I.M. or S.C. This dose may be repeated in accordance with the adult administration guideline. If necessary, NARCAN® (naloxone hydrochloride) can be diluted with sterile water for injection.

USAGE IN NEONATES Narcotic-induced depression The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines.

HOW SUPPLIED 0.4 mg/ml of NARCAN® (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration.

Available in 1 ml ampuls in boxes of 10 and 100.

0.02 mg/ml of NARCAN® (naloxone hydrochloride) NEONATAL INJECTION for intravenous, intramuscular and subcutaneous administration.

Available in 2 ml ampuls in boxes of 10 and 100 ampuls.

ANIMAL PHARMACOLOGY AND TOXICOLOGY In the mouse and rat the intravenous LD_{50} is 150 ± 5 mg/kg and 109 ± 4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the LD_{50} (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injections; no toxic effects were seen at 10 mg/kg/day for 3 weeks.

Reproductive studies including fertility, general reproductive performance, embryotoxicity, teratogenicity and lactation did not show any abnormality in mice and rats at 10 mg/kg/day.

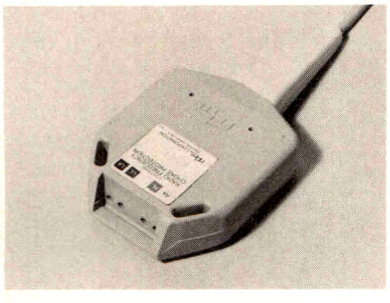
NARCAN® (naloxone hydrochloride) Ampuls
Stocked in Military Depot, NSN 6505-00-079-7867

Endo Laboratories, Inc.
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DUPONT

76-1 EDO-6040

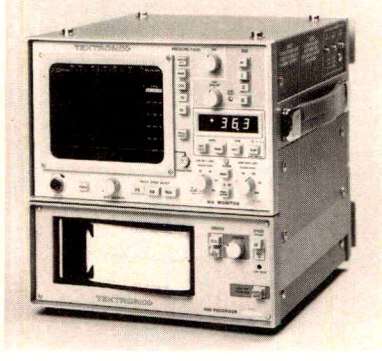
SOMETHING NEW

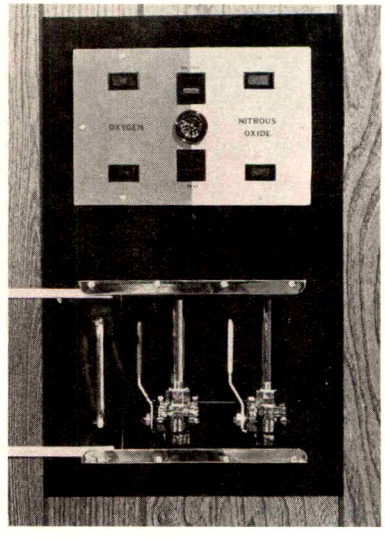


Protection against radio frequency burns at ECG electrode sites as a result of electrosurgery is provided by the RF Choke cable, which incorporates a radio frequency choke (inductor) in series with each monitoring lead. It is available from the NDM Hospital Supply, Dayton, Ohio. According to the manufacturer, the RF Choke cable will effectively block the passage of electrosurgical current through ECG leads, thereby reducing this radio frequency patient burn hazard. Cables are available to fit most of the ECG monitors currently in use in the United States.

★ ★ ★

Permanent hard copies of monitored patient data are available in a portable format with Tektronix' new 400-Series Recorders. These compact recorders attach directly to the company's portable patient monitors without a separate power cord or external interconnect wiring. The entire 18 lb. monitor-recorder package may be hand-carried and will operate on either AC line or the monitor's internal battery pack.

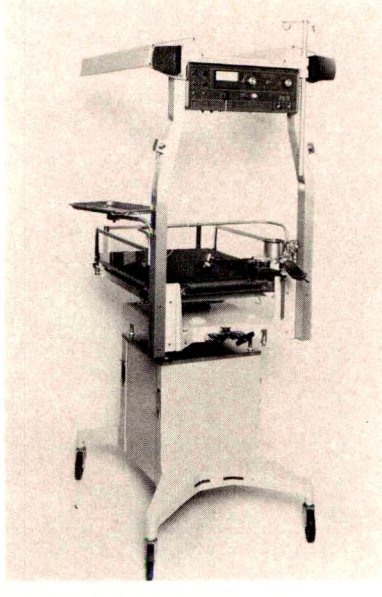




McKesson, Moncks Corner, South Carolina, introduces a Hi/Lo Warning System for conscious dental sedation systems. The system is spliced into the main oxygen and nitrous oxide piping lines and if in-line pressure drops or fails, or rises above normal operating ranges, an audible alarm is sounded and a visual warning mode illuminated. It responds to variations of about 20% above or below normal (50 to 55 psig) set points.

It is claimed that the McKesson Hi/Lo Warning System meets or surpasses all standards established by the National Fire Protection Association for N_2O and O_2 warning systems and zone valves.

★ ★ ★



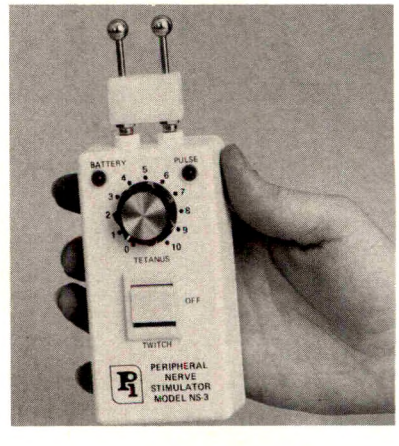
Ohio Medical Products, Madison, Wisconsin, has introduced an operating room model of their Neonatal Intensive Care Center designed to meet the specific needs of the surgeon and anesthetist. The new N.I.C.C. unit incorporates the essential life support systems and complete infant accessibility of the other OHIO units, while offering optimum surgical procedural capability.

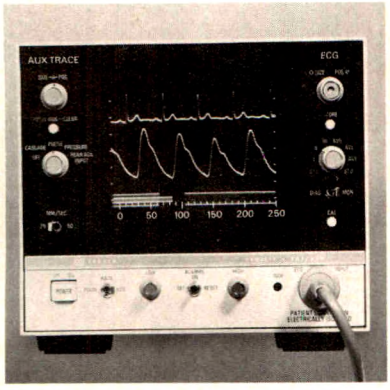
The N.I.C.C. control console, which incorporates the infant "Servo" temperature control module, indicator lights and necessary alarm signals, has been repositioned for observation by the anesthetist during the surgical procedure.

An adjustable anesthesia screen support is included that can be removed when not needed. The rear stainless steel bed rail has been replaced with a 2-inch wide, mattress height panel, for the convenience of the anesthetist.

★ ★ ★

Professional Instruments Company, Inc., Houston, Texas, have added the Model NS-3 to its line of Peripheral Nerve Stimulators. The NS-3 features monophasic square wave stimulus pulses of short duration and a low battery voltage indicator. The instrument may be used with ball-type electrodes, hypodermic needles or pregelled electrodes.



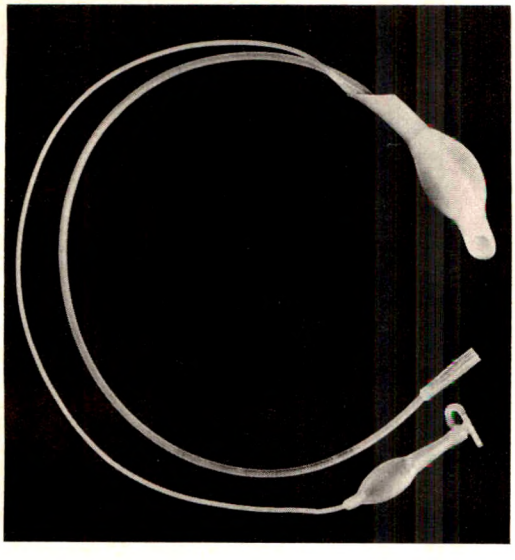


Multiparameter monitoring, including ECG, EEG, pulse and heart rate, is offered on a new Hewlett-Packard two-channel patient monitor. When used with external processing amplifiers, pressure and respiration also may be displayed simultaneously with the ECG tracing.

The HP 78332A monitor has bright, nonfade displays and operates in either fixed or moving-trace modes. Waveforms may be held on the screen for closer examination or the ECG display time may be doubled by continuing the upper channel information on the auxiliary channel. Useful in studying time/event relationships, the unit can superimpose ECG waveforms and auxiliary-channel information such as pulse pressure or respiration waveforms. Heart rate is indicated by a lighted bar graph.

The diagnostic or monitoring bandwidth is switch selectable to adjust fine detail in the display trace. Other simple-to-use controls alter size, position, intensity and sweep speed of the trace and allow calibration and selection of the heart-rate source. An optional beeper sounds when a preset alarm level has been reached or when an R wave is detected. Using pitch variation, the beeper also serves as an audible arrhythmia detection system.

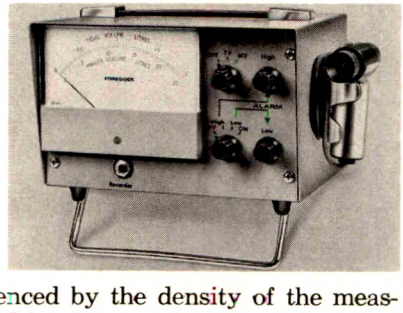
★ ★ ★



The Surgitek® Carden Laryngoscopy tube is now available with the exclusive Surgitek® Low trauma cuff from Medical Engineering Corporation, Racine, Wisconsin. It is claimed that these all silicone tubes are much less likely to cause necrosis than are tubes manufactured from PVC, Latex or red rubber. The Surgitek® tubes are reuseable and may be steam or gas sterilized.

★ ★ ★

The FOREGGER® 510 Electronic Spirometer, a low-cost, unidirectional spirometer that monitors continuous ventilation and measures intermandatory ventilation (IMV) has been introduced by Air Products and Chemicals, Inc., Allentown, Pennsylvania.



This unit provides an accurate means of measuring patient tidal and minute volume during continuous or intermittent ventilation. When placed in the expiratory side of a patient's breathing circuit, the FOREGGER spirometer's specially-designed, unidirectional sensor accurately reads the volumetric—instead of mass-flow rate of a gas. Resulting measured values are not influenced by the density of the measured gas or gas mixtures. Accuracy is claimed to be within plus or minus five percent of the indicated value.

INJECTION, equivalent to 10 mg metaraminol per ml

Aramine® (Metaraminol Bitartrate | MSD)

a vasopressor with positive inotropic effect

Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:
Effective: ARAMINE is indicated for prevention and treatment of the acute hypotensive state occurring with spinal anesthesia. Adjunctive treatment of hypotension due to hemorrhage; reactions to medications; surgical complications; and shock associated with brain damage due to trauma or tumor.
"Probably" effective: It may also be useful as an adjunct in the treatment of hypotension due to cardiogenic shock or septicemia.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Use should be avoided with cyclopropane or halothane anesthesia, unless clinical circumstances demand such use.

Precautions: Use with caution to avoid excessive blood pressure response. Rapidly induced hypertensive responses have been reported to cause acute pulmonary edema, arrhythmias, and cardiac arrest. Use with caution in digitalized patients, since the combination of digitalis and sympathomimetic amines is capable of causing ectopic arrhythmic activity. Treat cirrhotic patients cautiously; if diuresis ensues, restore electrolytes. Fatal ventricular arrhythmia has been reported in one patient with Laennec's cirrhosis. In several instances, ventricular extrasystoles that appeared during infusion have subsided promptly on reduction of infusion rate. Since metaraminol has prolonged duration of action, a cumulative effect is possible, leading to prolonged elevation of blood pressure even with discontinuation of therapy. Monoamine oxidase inhibitors have been reported to potentiate action of sympathomimetic amines.
When vasopressor amines are used for long periods, resulting vasoconstriction may prevent adequate expansion of circulating volume and may cause perpetuation of the shock state. Plasma volume may be reduced in all types of shock, and measurement of central venous pressure is the most useful means of assessing the adequacy of the circulating blood volume; blood or plasma volume expanders should be employed for hypotension or shock due mainly to decreased circulating volume. Because of its vasoconstrictor effect, metaraminol should be used with caution in heart or thyroid disease, hypertension, or diabetes. Sympathomimetic amines may provoke relapse in patients with history of malaria.

Adverse Reactions: Sinus or ventricular tachycardia, or other arrhythmias, especially in patients with myocardial infarction. Abscess formation, tissue necrosis, or sloughing may rarely follow use. In choosing the site of injection, it is important to avoid those areas recognized as *not* suitable for use of any pressor agent, and to discontinue infusion immediately if infiltration or thrombosis occurs. The larger veins of the antecubital fossa or the thigh are preferred to veins in the dorsum of the hand or ankle veins, particularly in patients with peripheral vascular disease, diabetes mellitus, Buerger's disease, or conditions with coexistent hypercoagulability.

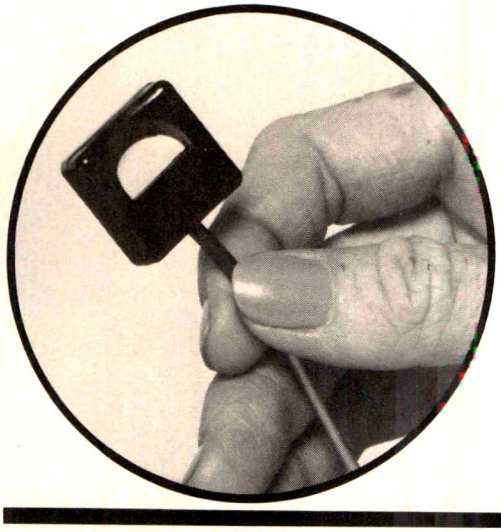
Note: Response to vasopressors may be poor in patients with coexistent shock and acidosis. Established methods of shock management, such as blood or fluid replacement when indicated, and other measures directed to the specific cause of the shock state also should be used. *Only Sodium Chloride Injection or 5 percent Dextrose Injection should be used as a diluent.*

How Supplied: Injection, in 1-ml ampuls and 10-ml vials, containing per ml: metaraminol bitartrate equivalent to 10.0 mg metaraminol; inactive ingredients: sodium chloride, 4.4 mg; water for injection, q.s. ad 1.0 ml; and 0.15% methylparaben, 0.02% propylparaben, and 0.2% sodium bisulfite added as preservatives.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

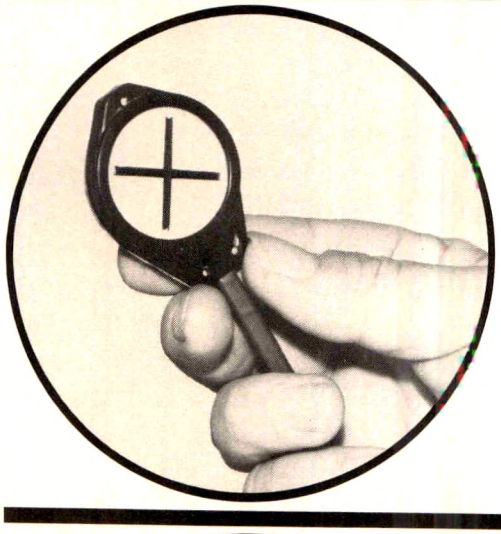
MSD
MERCK SHARP & DOHME

VERSATONE® MULTI-PURPOSE DOPPLER INSTRUMENT



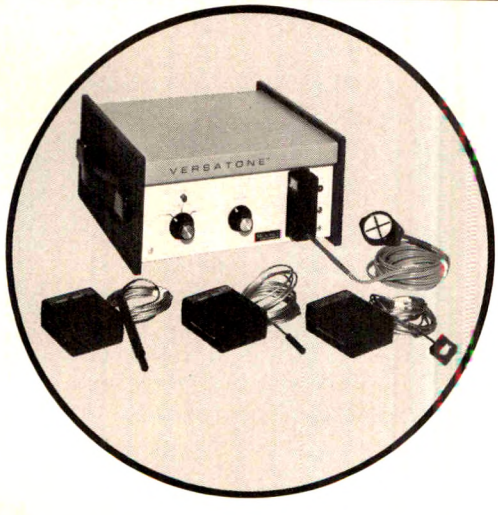
FOR MONITORING DOPPLER SOUNDS OF BLOOD FLOW AND TO TAKE DOPPLER SYSTOLIC BLOOD PRESSURE

This sensitive Doppler probe is easy to tape in position for non-invasive detection and monitoring of arterial blood flow during surgery. Used with an occlusive cuff and manometer, systolic blood pressures may be obtained even on infants and hypotensive patients.



FOR EARLY DETECTION OF VENOUS AIR EMBOLISM

This sensitive wide-angle Doppler probe is particularly well suited for the detection of venous air emboli which may occur during neurosurgical procedures performed with the patient in the upright position. It also detects motion of the heart muscle, heart valves and blood flow.



VERSATONE D8 DOPPLER

The Model D8 VERSATONE Doppler instrument is designed to use interchangeable probes of various frequencies and configurations. It is powered by a rechargeable battery and has a built-in loudspeaker. Options include an electrocautery sensor and cut-out, a molded earset for private listening, and a chart recording circuit. The two probes shown above are particularly useful to the anesthesiologist. Two sizes of pencil shaped probes are also available. These are useful for intraoperative assessment of flow in exposed vessels, as well as for transcutaneous flow detection.

MED SONICS
For more information call or write:
P.O. Box M (340 Pioneer Way) Mountain View, CA (415) 965-3333

PI Peripheral Nerve Stimulator

Monitors Muscle Relaxants

The PI Peripheral Nerve Stimulator monitors effects of skeletal muscle relaxants on the neuromuscular junction, detects abnormal response to muscle relaxants and distinguishes between depolarizing and non-depolarizing blockade.

Model NS-2

The NS-2 is now in use in many hospitals throughout the U. S. and abroad. It is designed primarily for use during surgery and delivers stimuli automatically at 5-second intervals. One or fifty pulses-per-second may be selected by momentary push-button switches. Output is a monophasic square wave pulse. Amplitude of the pulse is linearly adjustable. A flashing red light indicates low battery voltage. The NS-2 is solid state, rugged, battery powered, portable and lightweight.

Model NS-3

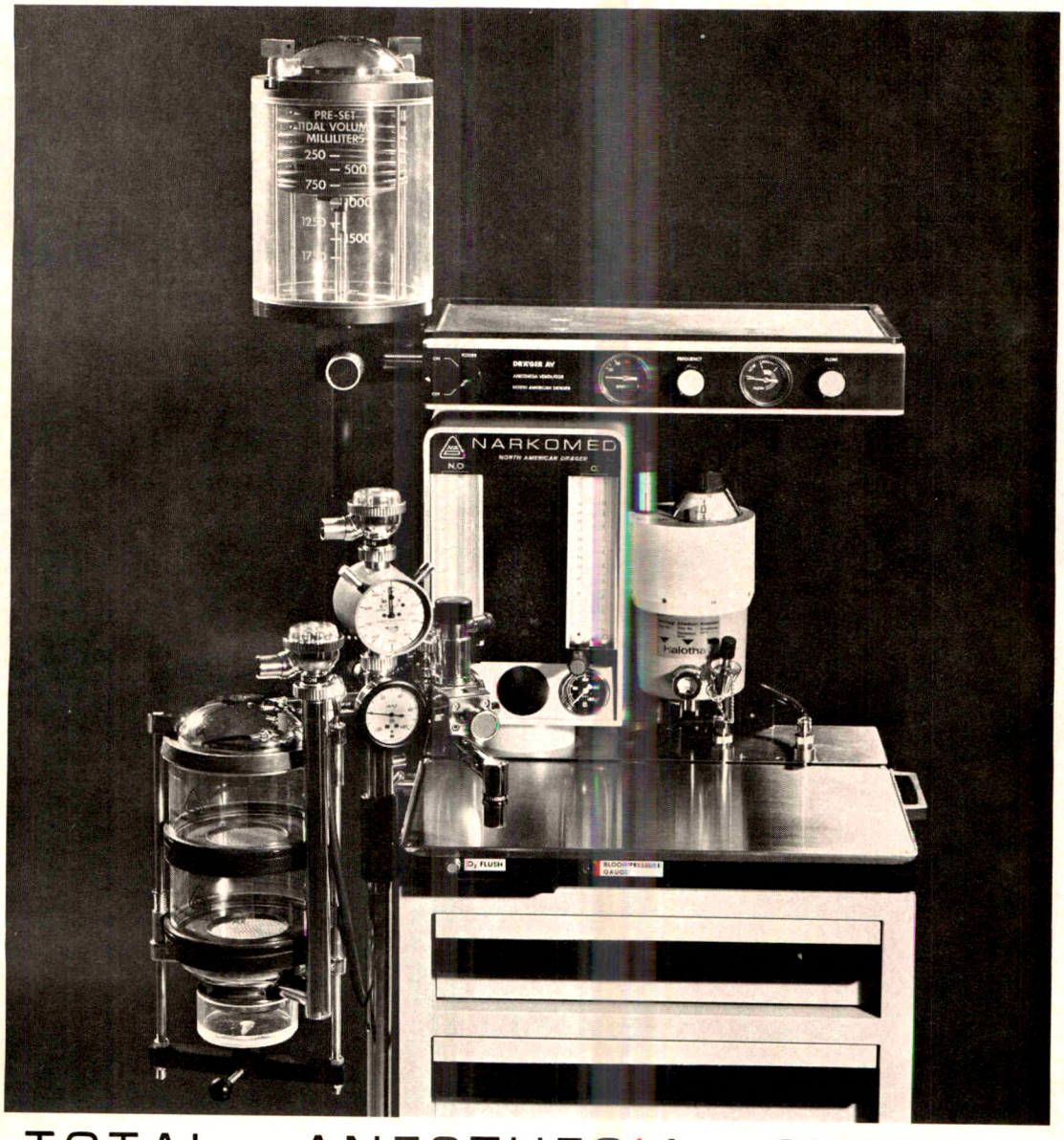
The NS-3 represents the latest in solid state technology. Use of integrated circuits has made it possible to build a very compact and versatile stimulator. Its miniature size makes the NS-3 more convenient for preoperative and postoperative testing. It delivers stimili at one second intervals when the rocker switch is depressed to the TWITCH position. A fifty-pulses-per-second rate may be selected by depressing the rocker switch to the momentary TETANUS position. Output is a monophasic square wave pulse. Amplitude of the pulse is linearly adjustable. The NS-3 also has a low-battery-voltage indicator.

Professional Instruments Company

General Office and Sales
Brookhollow Plaza, Suite C-5, 4800 W. 34th Street
P.O. Box 38245, Houston, Texas 77092

Professional Medical and Scientific Instrumentation

NARKOMED



TOTAL ANESTHESIA SYSTEM

NARKOMED, a refreshing new concept in anesthesia machine design and styling, incorporating a contemporary anesthesia dispensing system with a built-in fluidic anesthesia ventilator and the widest variety of options.

Please return the accompanying coupon for further information.

NORTH AMERICAN DRÄGER

NORTH AMERICAN DRÄGER

P.O. Box 121
Telford, Pa. 18969

____ Please send information on the NARKOMED TOTAL ANESTHESIA SYSTEM
____ Please include a copy of Anesthesia Accessories Catalog
____ Please send information on _____

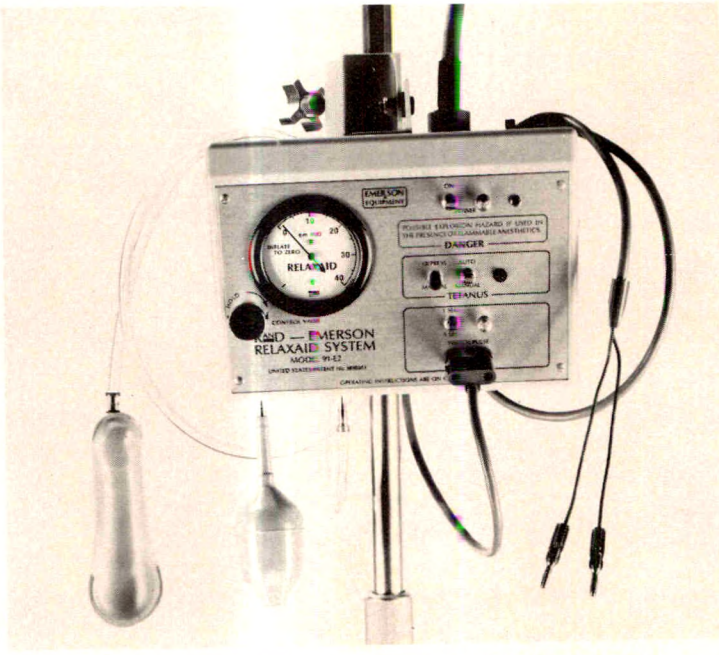
NAME _____

TITLE _____

HOSPITAL _____

ADDRESS _____

R AND D-EMERSON RELAXAID ™



for CORRECT RELAXANT DOSAGE—
AVOIDANCE OF OVERDOSE—
PROMPT RECOVERY—

The stimulator is programed to deliver pulses, through electrodes, to the ulnar nerve. A flexible pneumatic bulb is placed in the patient's hand, with his fingers held against it by tape. The bulb is then air-filled to a pressure of 20 cm. H_2O. As the fingers flex, even slightly, compression of the bulb is registered on an aneroid gauge. The pattern of these responses keeps the anesthetist informed of the relaxant's effectiveness.

The more precise monitoring provided by the RELAXAID™ enables relaxant levels to be kept adequate but without overdose. During recovery the RELAXAID™ shows the return of strength to the patient's muscles.

Please request Form 91-E2

J. H. EMERSON COMPANY
CAMBRIDGE, MASSACHUSETTS 02140

Non-conductive blood pressure cuffs . . . in color!

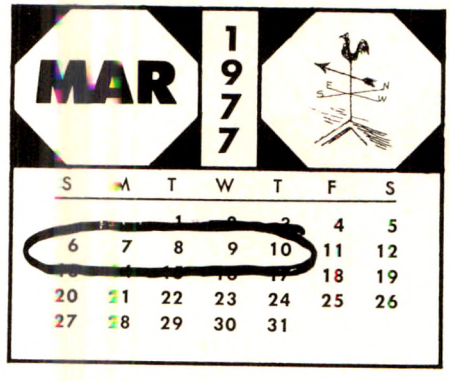
Color-code your departments! Dupaco offers high quality non-conductive blood pressure cuffs in red, blue denim, paisley or plaid. Monogramming available up to 20 stitched letters, with department or individual's name.

Stain resistant, washable, with velcro attaching strips for Dupaco Diasyst.® Sizes listed below. For more information write: Dupaco Inc., P.O. Box 98, San Marcos, CA 92069.

Adult	5¾" x 22"
Medium Adult	5" x 17¾"
Child	3¾" x 14½"
Infant	2¾" x 11½"

DUPACO
INCORPORATED

MARK YOUR CALENDAR



51ST CONGRESS

International Anesthesia Research Society

MARCH 6-10, 1977

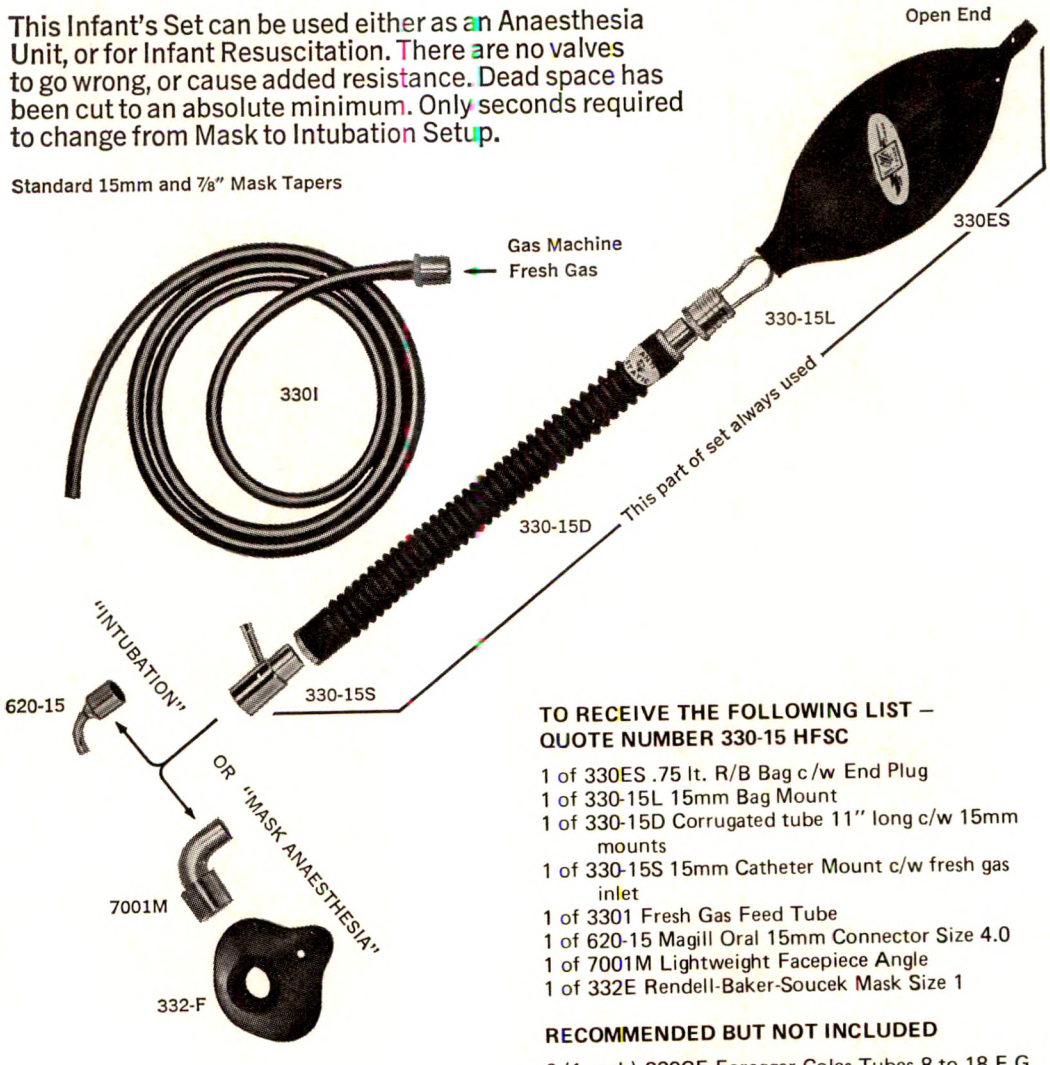
DIPLOMAT RESORT AND COUNTRY CLUBS
HOLLYWOOD, FLORIDA

JACKSON-REES MODIFICATION OF AYRE'S T-PIECE

as used by leading children's hospitals

This Infant's Set can be used either as an Anaesthesia Unit, or for Infant Resuscitation. There are no valves to go wrong, or cause added resistance. Dead space has been cut to an absolute minimum. Only seconds required to change from Mask to Intubation Setup.

Standard 15mm and 7/8" Mask Tapers



TO RECEIVE THE FOLLOWING LIST — QUOTE NUMBER 330-15 HFSC

1 of 330ES .75 lt. R/B Bag c/w End Plug
1 of 330-15L 15mm Bag Mount
1 of 330-15D Corrugated tube 11" long c/w 15mm mounts
1 of 330-15S 15mm Catheter Mount c/w fresh gas inlet
1 of 3301 Fresh Gas Feed Tube
1 of 620-15 Magill Oral 15mm Connector Size 4.0
1 of 7001M Lightweight Facepiece Angle
1 of 332E Rendell-Baker-Soucek Mask Size 1

RECOMMENDED BUT NOT INCLUDED

6 (1 each) 330CF Foregger Coles Tubes 8 to 18 F.G.
1 No. 332F Rendell-Baker-Soucek Mask Size 2
1 No. 332L Rendell-Baker-Soucek Mask Size 3
1 330LC Leather Case
1 of 330-15D Corrugated tube c/w 15mm mounts.

We recommend you purchase a 330LC Leather Case to store this equipment — prevents loss or damage.

MIE

MEDICAL & INDUSTRIAL EQUIPMENT
A division of Claudius Ash Incorporated
655 - 73rd Street, Niagara Falls, New York 14304

SEND FOR COMPLETE LITERATURE

INDEX OF ADVERTISERS

Air Products and Chemicals, Inc. —*Trace Gas Monitor* ..... (68)
Allergan Pharmaceuticals—*Lacri-Lube*® ..... (37)
Applied Medical Research Corporation—*Dinamap* ..... (25)
Ayerst Laboratories—*Fluothane*® ..... (22), (23), (24)
Burroughs Wellcome Company—*Anectine*® ..... (6), (7)
Datascope Corp.—*Monitors* ..... (26)
Dupaco, Inc.—*Blood Pressure Cuffs* ..... (27)
Dupaco, Inc.—*Non-Conductive Blood Pressure Cuffs* ..... (63)
Dupaco, Inc.—*Opti-Gard*(TM) ..... (51)
Educational Review, Inc.—*Practical Reviews in Anesthesiology* ..... (11)
J. H. Emerson Company—*IMV Ventilator* ..... (62)
Endo Laboratories—*Narcan*® ..... (52), (53), (54)
Extracorporeal Medical Specialties, Inc.—*Lanz Endotracheal Tube* ..... (43)
Fenwal Laboratories—*Operating Room System* ..... (47), (48), (49), (50)
Harris-Lake, Inc.—*Laryngoscopes* ..... (2)
McNeil Laboratories, Inc.—*Innovar*® ..... (45), (46)
McNeil Laboratories, Inc.—*Sublimaze*® ..... (16), (17), (18)
Medical and Industrial Equipment Div., Claudius Ash, Inc.—
Jackson-Rees T-Piece ..... (64)
Medsonics, Inc.—*Versatone*® *Doppler* ..... (59)
Merck, Sharp & Dohme—*Aramine*® ..... (58)
North American Drager—*Narkomed Anesthesia Machine* ..... (61)
Ohio Medical Products—*Anesthesia System* ..... (12), (13)
Ohio Medical Products—*Ethrane*® ..... (34), (35), (36)
O'Neal, Jones & Feldman, Inc.—*Antilirium* ..... (38)
Parke, Davis & Company—*Ketalar* ..... (8), (9), (10)
Pennwalt Corp.—*Nesacaine*® ..... (28), (29)
Pharmaseal Laboratories—*Anesthesia Trays* ..... (66), (67)
Plasticast Laboratories, Inc.—*Custom Earmold* ..... (27)
Professional Instruments Company—*PI Nerve Stimulator* ..... (60)
Pulmonary Specialties, Inc.—*PSI 5000 Recorder* ..... (44)
A. H. Robins Company—*Dopram*® ..... (14), (15)
Schuemann Labs. (Rals Laboratories Division)—*Rals Power Unit* ..... (44)
Winthrop Laboratories—*Marcaine*® ..... (40), (41), (42)

When to use the word Phär′mà·sēal.

For components, features, "performance" in single-use anesthesia trays, just say the word.

The trays you've counted on from the start now offer you even more to go on.

Back in 1963 we introduced the world's first single-use, regional anesthesia trays.

Today, with a record of safe performance difficult to equal, we offer you an even wider selection of components and features—just as difficult to match—in spinal, caudal and epidural trays.

All with our all-new spinal needle. The needle that's been called the cleanest spinal needle yet. The one with a cannula with almost uncanny smoothness, a cartridge pack with an exceptional point protector, a matched-ground point, metal hub and more.

Trays that offer you a new fenestrated drape with its own adhesive tabs.

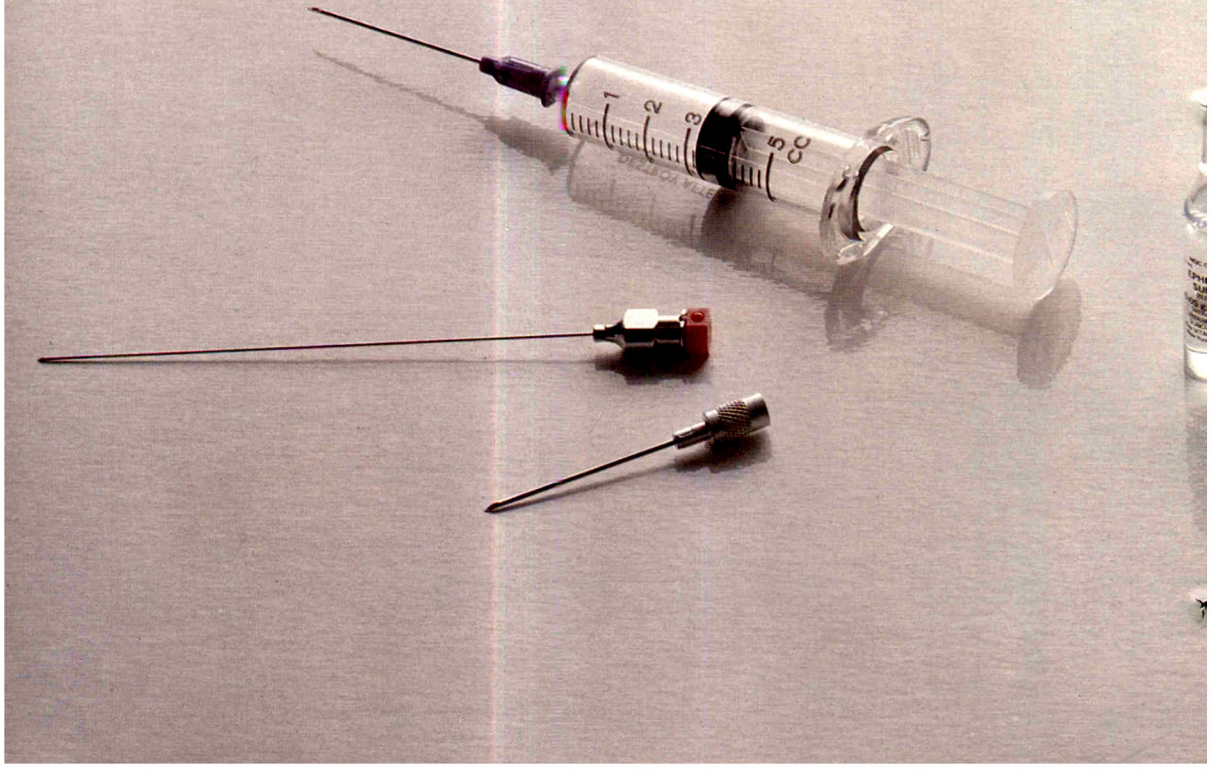
A large, moisture-resistant hospital wrap with a new "wrinkle" for better procedure.

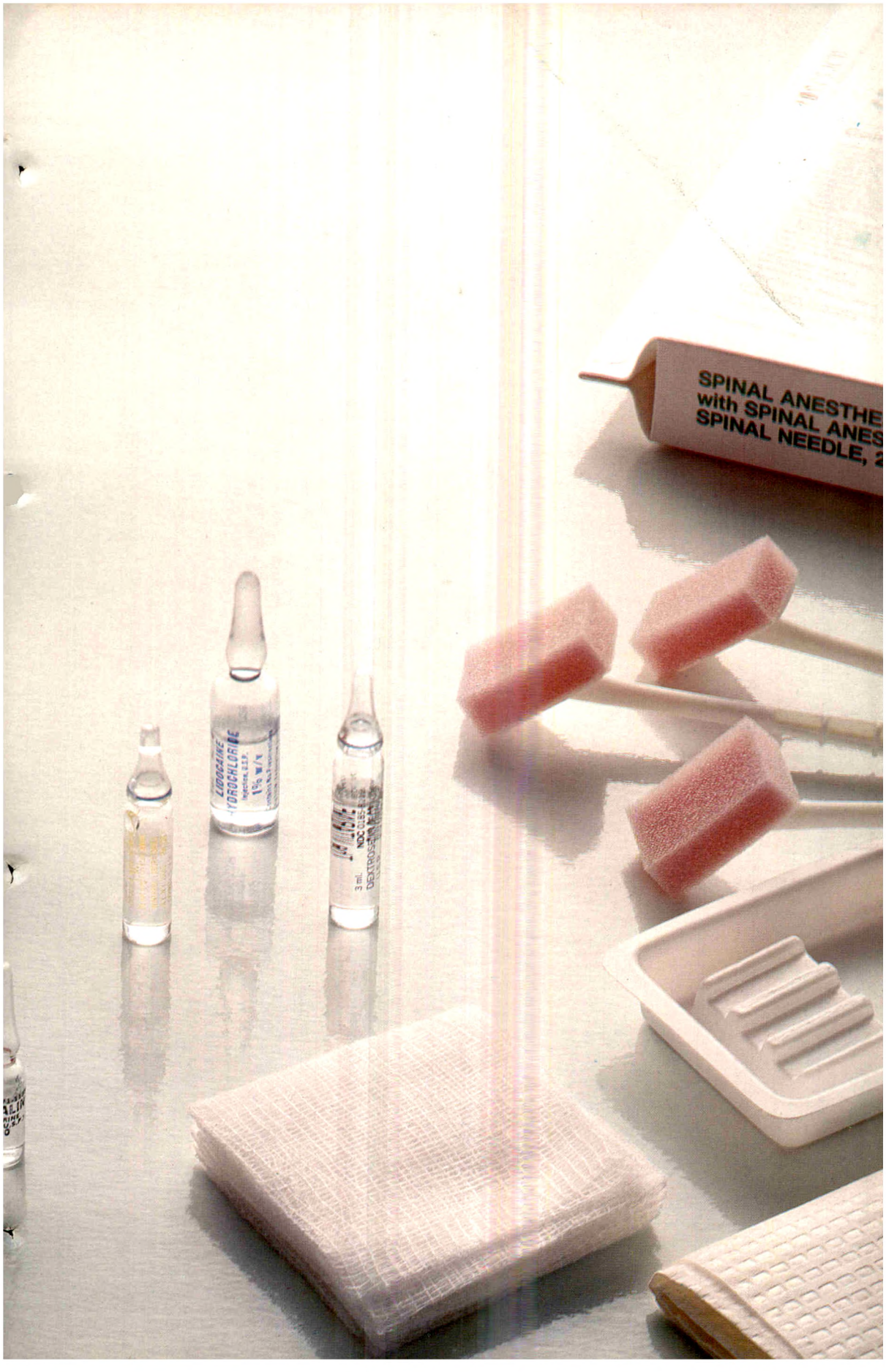
Plus, a specially designed introducer needle, a clear 5-cc. Stylex® syringe, a unique aseptic transfer carton...and a variety of other first-quality components and drugs.

But see for yourself what we're talking about. See the trays with performance you can count on. For samples, just call or write.

You know the word to use.

O.R./ANESTHESIA PRODUCTS BY
PHARMASEAL
GLENDALE, CALIFORNIA 91201




SPINAL ANESTHE
with SPINAL ANES
SPINAL NEEDLE, 2
LIDOCAINE
HYDROCHLORIDE
3 mL

If You're Confused About O.R. Pollution, Cut It Out.

Get a compilation of data on the problems of trace anesthetic gas and OR pollution control. Send for our Positive Response Program.

Besides reports and studies to help you put the problem in perspective, our "PRP" plan of action provides an up-to-date look at our products which help you detect and scavenge trace gas in your OR. Key to our program is the Foregger 410 N_2O Trace Gas Monitor, a basic requirement for any efficient trace gas monitoring program. It's designed to provide rapid and continuous sampling of the OR air you breathe.

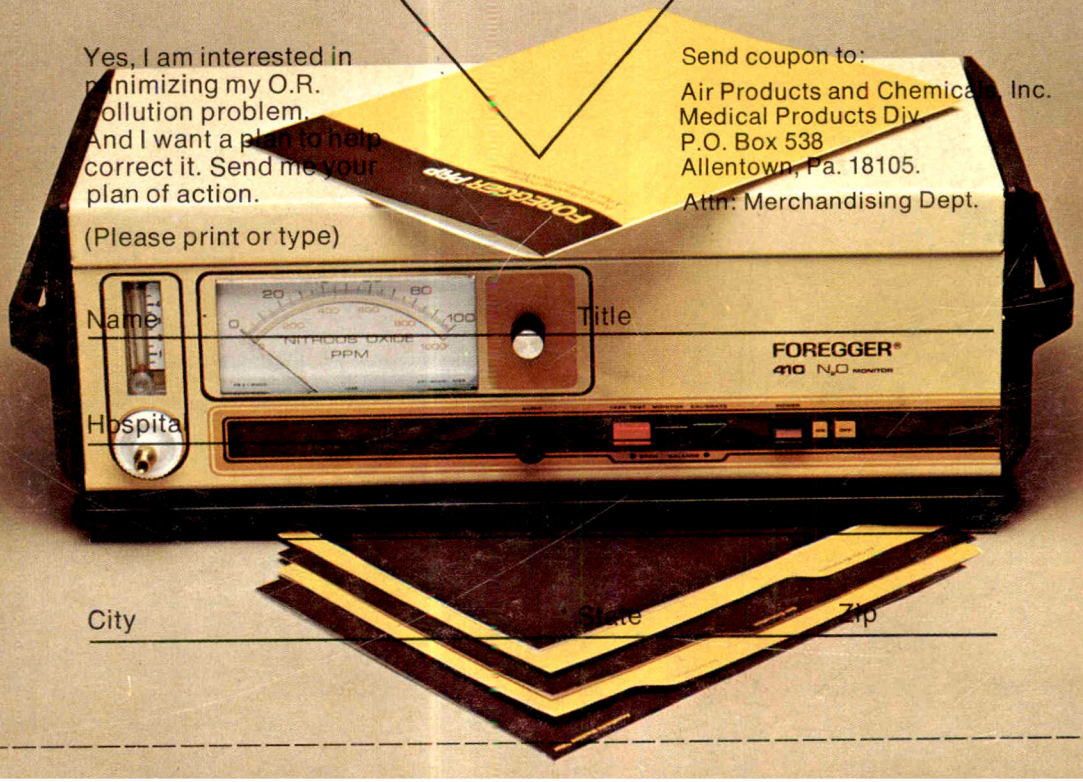
The machine has two sensing modes—Monitor (0-100 ppm) and Leak Test (0-1,000 ppm). The first mode continuously monitors the ambient air through the gas inlet of the machine. The second permits probing of local concentrations and sounds a repetitive burst alarm as the gas concentration increases.

In short, the Foregger 410 N_2O Trace Gas Monitor is a logical first step in solving your OR pollution problem. And there's more. The Scaveng-OR™ Gas Evacuator System, the Protect-OR™ Filter, Wall Suction Systems, and Air-CARE™ Preventive Maintenance Service.

Based on current data, it's likely that routine monitoring of pollution levels and scavenging of waste anesthetic gases will soon be standard Operating Room procedure. We're ready to help you now.

Fill out this ad coupon or ask our Representative for a Foregger PRP Folder. You'll get the problem in perspective and a plan of action to help correct it.

Air Products
FOREGGER



Yes, I am interested in minimizing my O.R. pollution problem. And I want a plan to help correct it. Send me your plan of action.

(Please print or type)

Name _____ Title _____

Hospital _____

City _____ State _____ Zip _____

Send coupon to:

Air Products and Chemicals, Inc.
Medical Products Div.
P.O. Box 538
Allentown, Pa. 18105.

Attn: Merchandising Dept.

Acc.
22.3.77

Anesthesia AND Analgesia

.....CURRENT RESEARCHES

Anesthesia for the Patient with Cardiac Disease:
Preamble ..... Page 617

A Comparative Interaction of Epinephrine with
Enflurane, Isoflurane and Halothane
in Man ..... Page 709

Table of Contents ..... Page (4)

Oldest Publication in the Specialty - Established 1922

Journal of the International Anesthesia Research Society

Volume 55, No. 5 September-October, 1976

51st Congress

Hollywood, Florida - March 6-10, 1977

Harlake® laryngoscopes

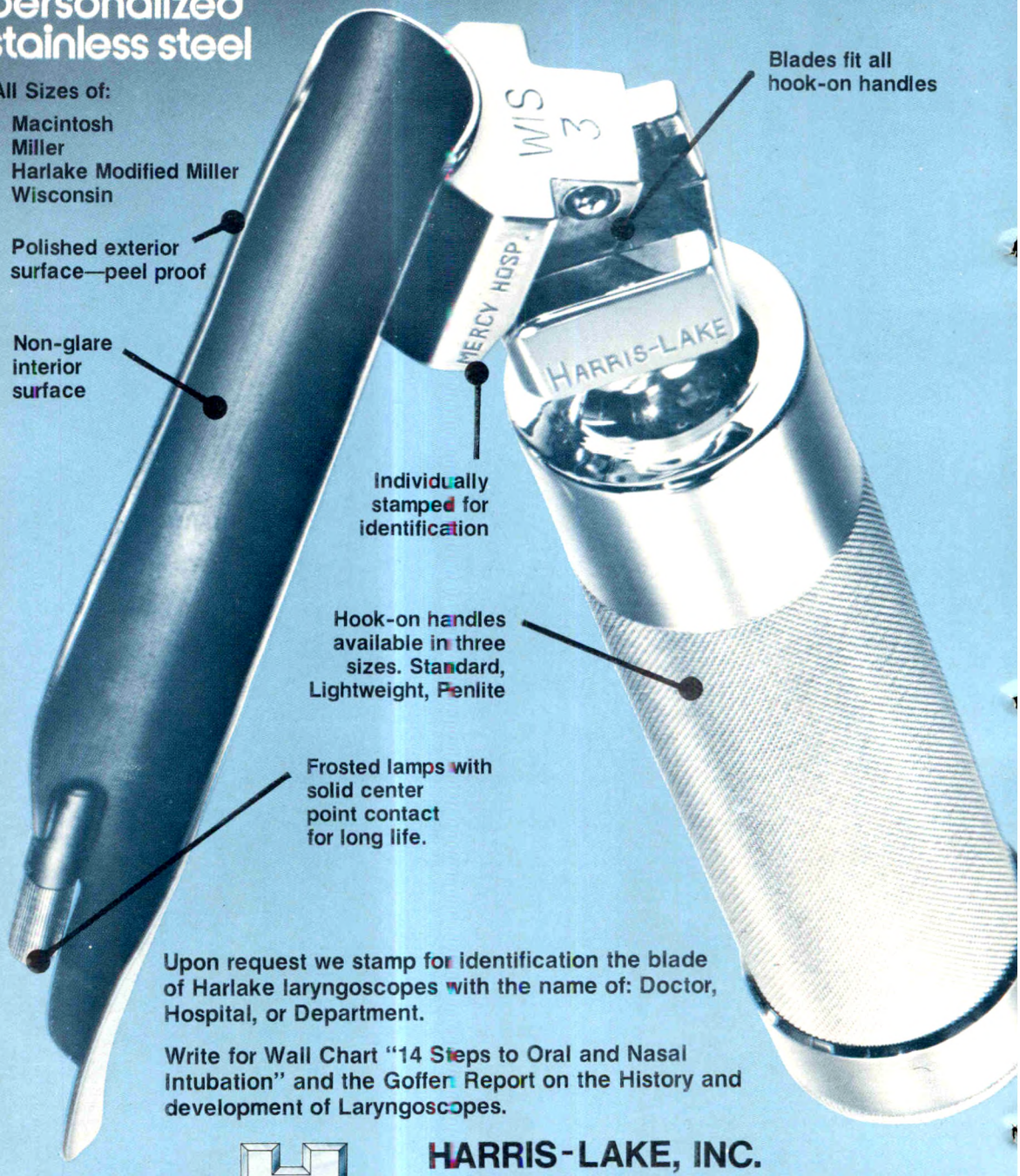
personalized stainless steel

All Sizes of:

Macintosh
Miller
Harlake Modified Miller
Wisconsin

Polished exterior surface—peel proof

Non-glare interior surface



Blades fit all hook-on handles

Individually stamped for identification

Hook-on handles available in three sizes. Standard, Lightweight, Penlite

Frosted lamps with solid center point contact for long life.

Upon request we stamp for identification the blade of Harlake laryngoscopes with the name of: Doctor, Hospital, or Department.

Write for Wall Chart "14 Steps to Oral and Nasal Intubation" and the Goffen Report on the History and development of Laryngoscopes.

HARRIS-LAKE, INC.

5600 South Marginal Road
Cleveland, Ohio 44103

A Medishield Company Medishield

Anesthesia AND Analgesia ...CURRENT RESEARCHES

JOURNAL OF THE INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

3645 Warrensville Center Road • Cleveland, Ohio, U.S.A. 44122 • Telephones: (216) 295-1124, 295-1130

EDITORIAL BOARD

Editor: T. H. Seldon, M.D., Rochester, Minnesota

Associate Editors:
John T. Martin, M.D., Toledo, Ohio
Emerson A. Moffitt, M.D., Halifax, Nova Scotia
Dean H. Morrow, M.D., Houston, Texas
Edwin S. Munson, M.D., Gainesville, Florida
Robert K. Stoelting, M.D., Indianapolis, Indiana

Contributing Editors:
Douglas B. Craig, M.D., Winnipeg, Manitoba
E. Paul Didier, M.D., Rochester, Minnesota
Ronald W. Dunbar, M.D., Atlanta, Georgia
Leonard C. Jenkins, M.D., Vancouver, British Columbia
David E. Longnecker, M.D., Charlottesville, Virginia
John J. Savarese, M.D., Boston, Massachusetts
N. Ty Smith, M.D., San Diego, California

ANESTHESIA AND ANALGESIA . . . Current Researches is published bimonthly by the International Anesthesia Research Society, a non-profit scientific and educational corporation of the state of Ohio. Members of the Board of Trustees of the Society are: Kenneth K. Keown, M.D., John T. Martin, M.D., Emerson A. Moffitt, M.D., Dean H. Morrow, M.D., Edwin S. Munson, M.D., B. B. Sankey, M.D., T. H. Seldon, M.D., Robert K. Stoelting, M.D. Emeritus Trustees are: Paul R. Dumke, M.D., Morris J. Nicholson, M.D.

EDITORIAL CORRESPONDENCE and manuscripts should be addressed to: **T. H. Seldon, M.D., Editor, Kahler East—Suite C, Rochester, Minnesota 55901, U.S.A. Telephone: (507) 288-8655.** (See "A Guide for Authors" for information concerning manuscript preparation.) Original articles accepted for publication, or papers presented at the Society's annual scientific meetings which are subsequently published in this Journal become the property of the International Anesthesia Research Society, publisher. Reproduction in whole or in part is not permitted except by written consent of the publisher and the author.

BUSINESS CORRESPONDENCE, including subscription and membership payments, single issue purchases, change of address notices, requests for membership applications, should be sent to: **B. B. Sankey, M.D., Executive Secretary and Business Manager, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122. Telephones: (216) 295-1124, 295-1130.**

SUBSCRIPTION RATE: $25.00 per year (6 issues), including postage.

MEMBERSHIP DUES: $25.00 per year, includes a subscription to the Journal. **Membership** available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine or other disciplines who are engaged either in active clinical practice of or research in anesthesiology. **Associate Membership** available to individuals certified, licensed or accredited in anesthesia-related professions (CRNA, ARIT, Physician Assistant). **Educational Membership** (two years for $25.00) available to interns, residents, students in nurse anesthesia and related training programs.

SINGLE ISSUES: $4.50 each for years beginning 1970; $3.00 for years 1954-1969; $2.00 for years 1928-1953. (See "Back Issues Available" or write to Cleveland business office for listing.)

REPRINTS: For single copies, write directly to senior author at address listed on title page. Quantity orders (minimum 100) processed through Cleveland business office, prices on request.

MAILING DATES: Journals mailed 25th of January, March, May, July, September and November. Second Class postage paid at Cleveland, Ohio.

CHANGE OF ADDRESS NOTICES: Send to Cleveland business office by first day of the above months to ensure correct addressing of Journals. Replacement copies of missing Journals will be furnished without charge only if original copy is returned by post office as undeliverable.

ADVERTISING: Rate sheets, including advertising clearance procedure, available from national advertising representative: Charles B. Slack, Inc., 6900 Grove Road, Thorofare, New Jersey 08086—Telephone: (609) 848-1000. Orders, contracts, reproduction materials, set copy and classified ad copy should be sent only to Cleveland office.

©1976, International Anesthesia Research Society.

Contents

Volume 55 September-October, 1976 Number 5

SCIENTIFIC ARTICLES

ANESTHESIA FOR THE PATIENT WITH CARDIAC DISEASE: PREAMBLE—Moffitt 617

THE PATIENT WITH HEART DISEASE: PREOPERATIVE EVALUATION AND PREPARATION—Goldberg 618

ANESTHETIC MANAGEMENT—Stevens 622

ANESTHESIA FOR PATIENTS WITH HEART BLOCK AND ARTIFICIAL CARDIAC PACEMAKERS—Wynands 626

DRUGS IN CARDIAC SUPPORTIVE CARE—White 633

ANESTHESIA FOR PATIENTS EARLY AFTER INFARCTION—Moffitt 640

PREANESTHETIC EVALUATION AND MANAGEMENT OF MALIGNANT HYPERTHERMIA IN THE PIG EXPERIMENTAL MODEL—Short, Paddleford, McGrath and Williams .. 643

SODIUM NITROPRUSSIDE-INDUCED HYPOTENSION FOR SUPINE TOTAL HIP REPLACEMENT—Lawson, Thompson, Nelson, Flacke and North 654

TRAIN-OF-FOUR FADE AND EDROPHONIUM ANTAGONISM OF NEUROMUSCULAR BLOCK BY SUCCINYLCHOLINE IN MAN—Lee 663

NEUTROPHIL CHEMOTAXIS DURING AND AFTER GENERAL ANESTHESIA AND OPERATION—Stanley, G. Hill, Portas, Hogan and H. Hill 668

HYPERTENSION AND DECREASED RENAL BLOOD FLOW FOLLOWING METHYLENE BLUE INJECTION—Birch and Boyce 674

HALOTHANE MAC IN DOGS UNCHANGED BY PHENOBARBITAL—Viegas and Stoelting 677

MASSIVE MYOGLOBINURIA PRECIPITATED BY HALOTHANE AND SUCCINYLCHOLINE IN A MEMBER OF A FAMILY WITH ELEVATION OF SERUM CREATINE PHOSPHOKINASE—Moore, Watson and Summary 680

THE EFFECTS OF HEPARIN ON RECOVERY FROM ISCHEMIC BRAIN INJURIES IN CATS—Stullken and Sokoll 683

CHANGE IN PULMONARY VENOUS ADMIXTURE WITH VARYING INSPIRED OXYGEN—Douglas, Downs, Dannemiller, Hodges and Munson 688

ABSENCE OF RECALL AFTER GENERAL ANESTHESIA: IMPLICATIONS FOR THEORY AND PRACTICE—Dubovsky and Trustman 696

EFFECT OF MORPHINE-DIAZEPAM ON SIGNS OF ANESTHESIA, AWARENESS, AND DREAMS OF PATIENTS UNDER N_2O FOR CESAREAN SECTION—Abouleish and Taylor 702

RELATION OF $Paco_2$ TO FRESH GAS FLOW IN A CIRCLE SYSTEM—Patel, Bennett, Grundy and Ignacio 706

A COMPARATIVE INTERACTION OF EPINEPHRINE WITH ENFLURANE, ISOFLURANE, AND HALOTHANE IN MAN—Johnston, Eger and Wilson 709

A PREPLANNED TREATMENT FOR MALIGNANT HYPERPYREXIA—Fraser, Crumrine and Izant 713

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
1922

Anesthesia AND Analgesia . . . Current Researches

SCIENTIFIC ARTICLES—September-October, 1976 (Continued)

THOUGHTS ABOUT MEDICAL WRITING. XXXVII. VERIFY YOUR REFERENCES—Roland . . 717

MAINTENANCE OF BODY TEMPERATURE BY HEATED HUMIDIFICATION—Tausk, Miller and Roberts 719

A COMPARISON OF THE EFFICIENCY OF THREE ANESTHESIA CIRCLE SYSTEMS—Harper and Eger 724

CLINICAL USE OF ETOMIDATE FOR ANESTHESIA INDUCTION: A PRELIMINARY REPORT—Fragen, Caldwell and Brunner 730

THE ANESTHETIC EFFECT OF OXYGEN—Smith and Paton 734

CASE HISTORY NUMBER 92: PROLONGED APNEA AFTER SUCCINYLCHOLINE IN A DENTAL OUTPATIENT—McLaren and Moffitt 737

BRIEF REPORTS

A PRECORDIAL ECG LEAD FOR CHEST OPERATIONS—Dalton 740

A SAFETY VALVE FOR THE PEDIATRIC REES SYSTEM—Ramanathan, Chalon and Turndorf 741

HAZARDS OF DISPOSABLE REBREATHING CIRCUITS—Cottrell, Bernhard and Turndorf 743

A PEEP DEVICE FOR A MANUAL BAG VENTILATOR—Perel, Eimerl and Grossberg 745

THE TRACHEAL BRONCHUS: AN UNUSUAL AIRWAY PROBLEM—Venkateswarlu, Turner, Carter and Morrow 746

INNOMINATE ARTERY COMPRESSION SIMULATING CARDIAC ARREST DURING MEDIASTINOSCOPY: A CASE REPORT—Lee and Salvatore 748

ANESTHESIA FOR VANISHING LUNG SYNDROME: REPORT OF A CASE—Isenhower and Cucchiara 750

FEATURES

People and Places . . . . . (9)

We Salute—
Lawrence F. Schuhmacher, Jr., M.D. 753

Correspondence:
Plastic-Covered Wire Stylet 755

Editor's Choice 756

The Physician and The Law 759

Questions and Answers 760

Book Shelf 762

Scientific Articles, Next Issue . . . . . (41)

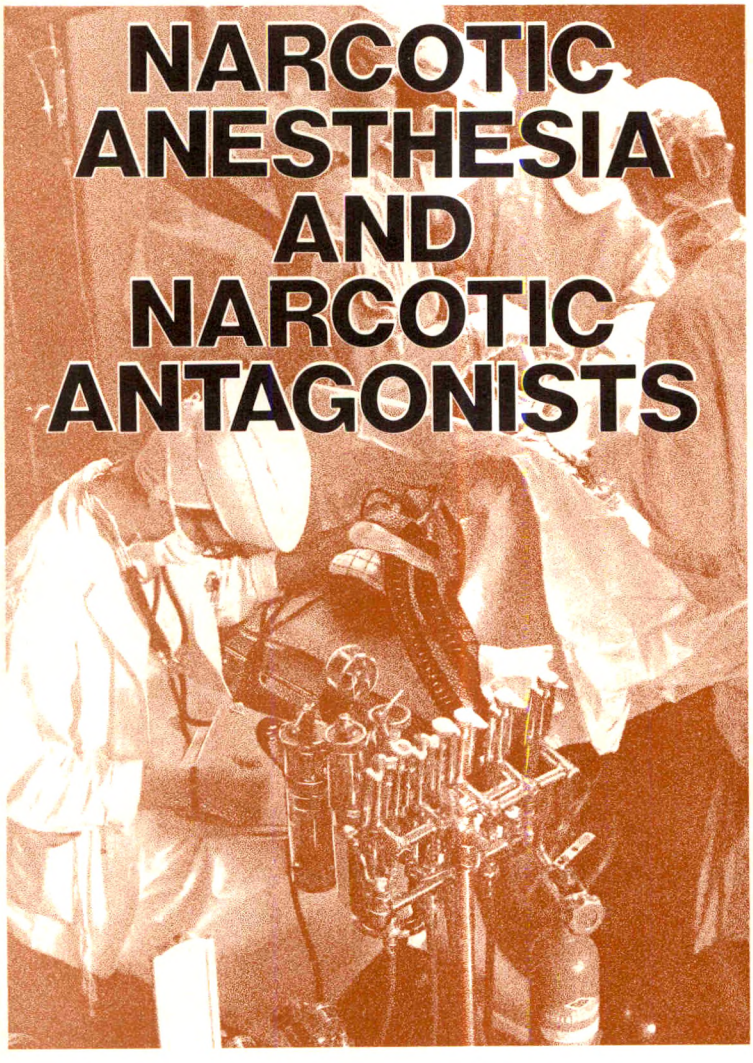
A Guide for Authors . . . . . (42)

Back Issues Available . . . . . (44)

Classified Advertising . . . . . (61)

Something New . . . . . (66)

Index of Advertisers . . . . . (71)



NARCOTIC ANESTHESIA

- Despite many advantages, the use of opioids to supplement nitrous oxide anesthesia may be associated with significant postoperative depression.

NARCAN® (naloxone HCl)

- Narcan® in sufficient doses will antagonize opioid effects, including all degrees of respiratory depression and analgesia.
- The degree of narcotic antagonism exhibited by NARCAN® is dose dependent.

A recent study of surgical patients receiving narcotic-nitrous oxide anesthesia was undertaken to determine whether careful titration of naloxone would reverse post-operative narcotic depression and maintain a subjective level of analgesia.[1]

THE OBJECTIVES:

- Restore consciousness
- Reverse narcotic-induced respiratory depression as evidenced by $PaCO_2$
- Maintain *subjective* analgesia

THE METHOD:

- 12 unpremedicated patients received INNOVAR® (fentanyl/droperidol) 5-10 ml I.V. followed by thiopental for induction. Anesthesia was maintained with N_2O-O_2. Increments of 0.1 mg *fentanyl* were given I.V. every 10 minutes during surgery.

Following the procedure, naloxone (0.1 mg/ml) was given in 0.1 mg I.V. increments at 1 minute intervals until the patient was awake, lucid and had adequate tidal and minute volumes. Additional naloxone

1. Heisterkamp DV, Cohen PJ: *Anesth Analg* (Cleve) 53:12-18, Jan-Feb 1974

NARCAN® is an Endo registered U.S. trademark; U.S. Pat. 3,254,088

was given I.V. as needed in the first 6 patients; a second group of 6 patients received supplemental naloxone I.M. 30 minutes after the initial I.V. dose.

- 11 patients received 10 mg *morphine* I.M., as well as secobarbital and atropine, 1½ hours preoperatively. Anesthesia was induced by 30 mg morphine given slowly I.V. followed by thiopental and was maintained by N_2O-O_2. Additional morphine was given in divided increments to total 1 mg/kg in the first hour. Further morphine was given as needed. For initial narcotic reversal, naloxone was given as above except at 2 minute intervals. Supplemental naloxone was given I.M. 30 minutes later.

THE RESULTS (fentanyl group):

- When fentanyl was used as the sole narcotic supplement during anesthesia, an I.M. dose of naloxone equal to half the I.V. reversal dose and given ½ hour later provided adequate narcotic reversal.

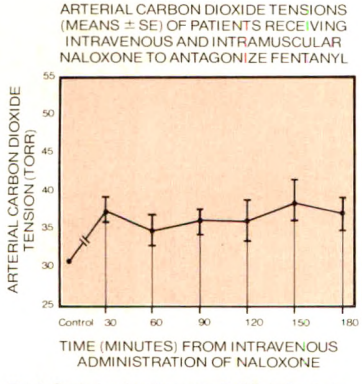


Fig. 1. Control and postoperative $PaCO_2$ in 6 patients receiving I.V. and I.M. naloxone following fentanyl.

THE RESULTS (morphine group):

- "After other narcotics, such as morphine, an I.M. dose of naloxone equal to the I.V. dose appears appropriate."

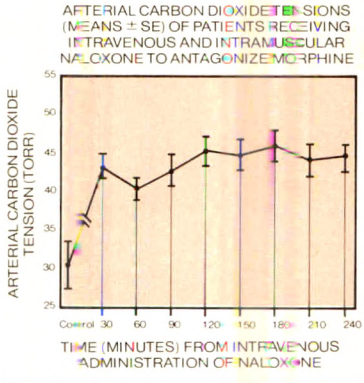


Fig. 2. Control and postoperative $PaCO_2$ in 6 patients receiving I.V. and I.M. naloxone following morphine.

THE CONCLUSIONS:

- "Naloxone provides fast, potent, and reliable antagonism to narcotic-induced respiratory depression."
- "By careful titration, this antagonism can be achieved while acceptable analgesia is maintained."
- "Both morphine and fentanyl groups had adequate analgesia, with only 2 patients [of total 21] requiring pain medication in the recovery room."

- **reverses all degrees of narcotic-induced respiratory depression**
- **does not cause narcotic-like effects**
- **does not augment non-narcotic depression**
- **acts rapidly—generally within 2 minutes following I.V. use and slightly less rapidly when given I.M.**
- **does not lead to tolerance**
- **does not produce psychotomimetic effects or pupillary constriction**
- **can be repeated if initial dose doesn't produce desired degree of narcotic reversal and improvement in respiratory function**
- **following satisfactory response patient should be observed closely and given repeat doses, if necessary, since the duration of action of some narcotics may exceed that of NARCAN®**

Please see next page for complete prescribing information.

Endo Laboratories, Inc.
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530
DUPONT

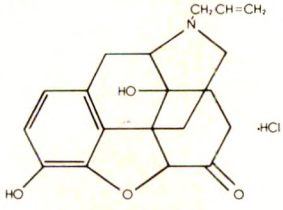
·restored consciousness
·reversed narcotic-induced respiratory depression
·maintained subjective analgesia

NARCAN®
(naloxone HCl)

can reverse narcotic-induced respiratory depression while maintaining subjective analgesia

NARCAN® (naloxone HCl)

DESCRIPTION NARCAN® (naloxone hydrochloride), a narcotic antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



NALOXONE HYDROCHLORIDE
(N-allyl-nor-oxymorphone HCl)

Naloxone hydrochloride occurs as slightly off-white crystals, and is soluble in water, slightly soluble in alcohol and practically insoluble in ether.

NARCAN® (naloxone hydrochloride) Injection is available in two concentrations, 0.02 mg and 0.4 mg of naloxone hydrochloride per ml. Each ml of either strength contains 8.6 mg of sodium chloride; and 2.0 mg of methylparaben and propylparaben as preservatives in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

ACTIONS NARCAN® (naloxone hydrochloride) is an essentially pure narcotic antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists; NARCAN® (naloxone hydrochloride) does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists it exhibits essentially no pharmacologic activity.

In the presence of physical dependence on narcotics NARCAN® (naloxone hydrochloride) will produce withdrawal symptoms; it has not been shown to produce tolerance nor to cause physical or psychological dependence.

When NARCAN® (naloxone hydrochloride) is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of NARCAN® (naloxone hydrochloride). Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of NARCAN® (naloxone hydrochloride), however, will also be dependent upon the amount, type and route of administration of the narcotic being antagonized.

INDICATIONS NARCAN® (naloxone hydrochloride) is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by natural and synthetic narcotics, propoxyphene and the narcotic-antagonist analgesic pentazocine.
NARCAN® (naloxone hydrochloride) is also indicated for the diagnosis of suspected acute opiate overdosage.

CONTRAINDICATIONS NARCAN® (naloxone hydrochloride) is contraindicated in patients known to be hypersensitive to it.

WARNINGS NARCAN® (naloxone hydrochloride) should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN® (naloxone hydrochloride) should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride).

NARCAN® (naloxone hydrochloride) is not effective against respiratory depression due to non-opioid drugs.

Usage in Pregnancy Safe use of NARCAN® (naloxone hydrochloride) during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or other embryotoxic effects (See ANIMAL PHARMACOLOGY AND TOXICOLOGY). However, NARCAN® (naloxone hydrochloride) should be administered to pregnant patients only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS In addition to NARCAN® (naloxone hydrochloride), other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

In an isolated report two patients with pre-existing ventricular irritability requiring lidocaine, and either isoproterenol or epinephrine for hypotension following cardiopulmonary bypass procedures, developed ventricular tachycardia or fibrillation when given NARCAN® (naloxone hydrochloride) I.V. at 9 and 14 hours, respectively, postoperatively for persistent unresponsiveness. Although a direct cause and effect relationship has not been established, NARCAN® (naloxone hydrochloride) should be used with caution in patients with cardiac irritability.

ADVERSE REACTIONS In rare instances nausea and vomiting have been reported in postoperative patients receiving NARCAN® (naloxone hydrochloride) in doses higher than that recommended; a cause and effect relationship has not been established.

DOSAGE AND ADMINISTRATION NARCAN® (naloxone hydrochloride) may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride) the patient should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary.

USAGE IN ADULTS Narcotic Overdose—Known or Suspected The usual initial adult dose is 0.4 mg (1 ml) NARCAN® (naloxone hydrochloride) administered I.V., I.M. or S.C. If the desired degree of counteraction and improvement in respiratory function is not obtained immediately following I.V. administration, it may be repeated intravenously at 2 to 3 minute intervals. Failure to obtain significant improvement after 2 or 3 doses suggests that the condition may be due partly or completely to other disease processes or non-opioid drugs.

Post Operative Narcotic Depression For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN® (naloxone hydrochloride) are usually sufficient. The dose of NARCAN® (naloxone hydrochloride) should be titrated according to the patient's response. Excessive dosage of NARCAN® (naloxone hydrochloride) may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or tachycardia.

For the initial reversal of respiratory depression, NARCAN® (naloxone hydrochloride) should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal i.e., adequate ventilation and alertness without significant pain or discomfort.

Repeat doses of NARCAN® (naloxone hydrochloride) may be required within one to two hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

USAGE IN CHILDREN Narcotic Overdose—Known or Suspected The usual initial child dose is 0.01 mg/kg body weight given I.V., I.M. or S.C. This dose may be repeated in accordance with the adult administration guideline. If necessary, NARCAN® (naloxone hydrochloride) can be diluted with sterile water for injection.

USAGE IN NEONATES Narcotic-induced depression The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines.

HOW SUPPLIED 0.4 mg/ml of NARCAN® (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration.

Available in 1 ml ampuls in boxes of 10 and 100.

0.02 mg/ml of NARCAN® (naloxone hydrochloride) NEONATAL INJECTION for intravenous, intramuscular and subcutaneous administration.

Available in 2 ml ampuls in boxes of 10 and 100 ampuls.

ANIMAL PHARMACOLOGY AND TOXICOLOGY In the mouse and rat the intravenous LD_{50} is 150 ±5 mg/kg and 109 ±4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the LD_{50} (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injections; no toxic effects were seen at 10 mg/kg/day for 3 weeks.

Reproductive studies including fertility, general reproductive performance, embryotoxicity, teratogenicity, and lactation did not show any abnormality in mice and rats at 10 mg/kg/day.

NARCAN® (naloxone hydrochloride) Ampuls
Stocked in Military Depot, NSN 6505-00-079-7867

Endo Laboratories, Inc.
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DUPONT

76-1 EDO-6040

PEOPLE and PLACES

The 14th Congress, Scandinavian Society of Anaesthesiologists, Uppsala, Sweden, will be held June 28-July 2, 1977. For information, write to The Institute for Continuing Education, P.O. Box 11083, Richmond, Virginia 23230.

★ ★

The New York State Society of Anesthesiologists celebrates its 30th Postgraduate Assembly in Anesthesiology December 5, 6, 7 and 8, 1976, at the New York Hilton Hotel. Inquiries should be directed to the Society at 30 East 42nd Street, Room 1501, New York, New York 10017

★ ★

The Third Annual Intermountain Conference on Critical Care: Maternal and Perinatal will be held February 12-19, 1977, at Sun Valley, Idaho.

This conference is sponsored by the Division of Continuing Medical Education, SC-50, University of Washington School of Medicine, Seattle, Washington and is C.M.E. accredited.

★ ★

The 6th Obstetric Anesthesia Conference, sponsored by the Los Angeles Obstetrical and Gynecological Society, will be held in Los Angeles on March 25, 26 and 27 and then continue for part II which will be at Del Webb's Kuilima resort hotel on the North Shore of Oahu, Hawaii, March 28-31, 1977.

A complete program, or further information, can be obtained by contacting **John S. McDonald, M.D.,** Obstetric Anesthesia, P.O. Box 7632, Fresno, California 93727.

★ ★

An opportunity for anesthesiologists and obstetricians/gynecologists to learn or review principles and practices of anesthesia and analgesia for obstetrics and gynecology is being offered in the Department of Anesthesiology at the Valley Medical Center in Fresno, California, under the direction of **John S. McDonald, M.D.,** Chairman of the Department. Four and eight week rotations would include general and regional anesthesia and didactic training in the pharmacology of drugs.

Applicants should be trained in the United States and must possess State or National Board Licensure. In some instances, foreign graduates who have passed the FLEX examination or the equivalent thereof will be considered. More information may be obtained by writing to **John S. McDonald, M.D.,** P.O. Box 7632, Fresno, California 93727.

The Third Annual Vail Conference in Anesthesiology will be held on February 5-12, 1977, at Lion Square Lodge—The Mark Resort in Vail, Colorado. For further information write to: **Sonja Auxier,** Professional Seminars, Inc., P.O. Box 236037, Miami, Florida 33123.

★ ★

The Fifteenth Biennial Western Conference on Anesthesiology, will be held May 15-19, 1977, at the Hyatt Regency Hotel, Embarcadero Center, San Francisco; followed by a Two-Day Refresher Course, May 20, 21 at the Del Monte Hyatt House, Monterey, California. All inquiries should be addressed to: Executive Secretary, B.W.C.A., 707-2525 Willow Street, Vancouver, B.C., Canada V5Z 3N8.

★ ★

The Fourth Neonatal and Infant Respiratory Symposium, sponsored by the California Society of Anesthesiologists, will be held at the Hyatt Hotel in Los Angeles, February 4 and 5, 1977, and at the Chateau Roaring Forks in Aspen, Colorado, February 6th through the 12th, 1977.

Section I, which is being held in Los Angeles, will consist of formal academic presentations and respiratory seminars. Section II, in Aspen, will be a more relaxed atmosphere, but academic presentations will be presented. This section will afford more indepth questioning and discussions.

A complete program or further information can be obtained by contacting **John S. McDonald, M.D.,** Perinatal Anesthesia, P.O. Box 7632, Fresno, California 93727.

★ ★

Childrens Hospital of Los Angeles, Division of Anesthesiology, will sponsor the Fifteenth Clinical Conference in Pediatric Anesthesiology on January 28, 29, and 30, 1977, at the Los Angeles Marriott Hotel, Los Angeles, California. For further information write to: **Wayne Herbert, M.D.,** Program Director, Pediatric Anesthesiology Conference, P.O. Box 54700, Los Angeles, California 90054.

★ ★

The 14th Annual Postgraduate Seminar in Anesthesiology will be held at the Americana Hotel, Miami Beach, Florida, on January 6-9, 1977. A Post-Convention Seminar is scheduled for January 9-15, in Aruba at the Tamarijn Hotel. For further information write: **Frank Moya, M.D.,** Department of Anesthesiology, Mt. Sinai Medical Center, Miami Beach, Florida 33140.

★ ★

"Clinical Pharmacology for Anesthesiologists" is the theme of the 22nd Annual Postgraduate Course of the University of Utah. This meeting will be held at the C'est Bon Hotel Convention Center, Park City, Utah, February 11-15, 1977.

★ ★

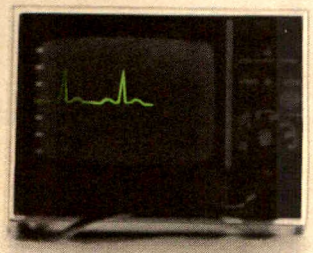
Clinical Advances in Pain Management, An Interdisciplinary Weekend Symposium, will be held October 23 and 24, 1976, at the Statler Hilton Hotel, New York City. For further information, contact: BioMonitoring Applications, Inc., Suite 1506, 270 Madison Avenue, New York, New York 10016.

★ ★

Anesthetic Management of the Surgical Patient sponsored by the Department of Anesthesiology, University of Miami School of Medicine—Caribbean cruise aboard S/S Royal Viking Sea, November 29 - December 12, 1976. Contact: **Sonja Auxier,** Department of Anesthesiology, University of Miami School of Medicine, P.O. Box 520875 Biscayne Annex, Miami, Florida 33152.

IN PORTABLE ECG MONITORS...

CONVENTIONAL TRACES FADE FAST



AMERICAN OPTICAL'S DURA-VUE® DISPLAY GIVES YOU MORE TIME TO SEE THE ECG EVENT YOU DON'T WANT TO MISS

HOW VALUABLE CAN THAT BE UNDER BUSY O.R. CONDITIONS?

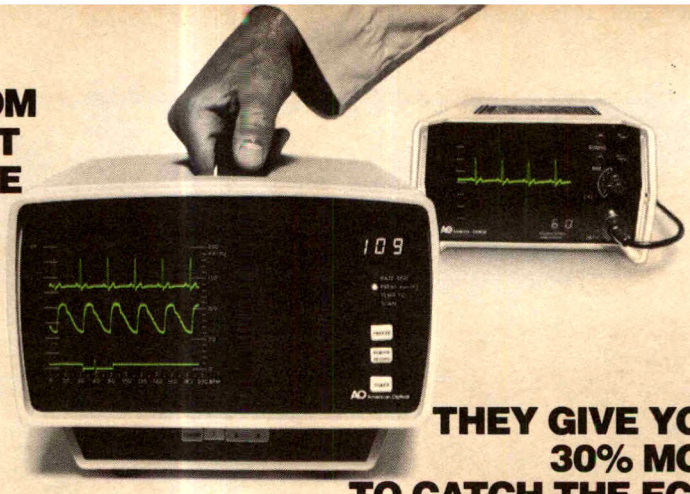
First Class
Permit No. 24
Bedford, MA

BUSINESS REPLY MAIL
No postage stamp necessary if mailed in the United States

Postage will be paid by:

American Optical MEDICAL DIVISION
Crosby Drive
Bedford, MA 01730

CHOOSE FROM 13 DIFFERENT AO PORTABLE MONITORS WITH DURA-VUE® DISPLAY



THEY GIVE YOU UP TO 30% MORE TIME TO CATCH THE ECG EVENT YOU DON'T WANT TO MISS

Line-Operated		Battery-Operated*
	ECG, Heart Rate, Systole Sound	1700
1600	ECG, Heart Rate, Alarms, Systole Sound	1601
1602	ECG, Digital Heart Rate, Alarms, Systole Sound	1603
1604	ECG, Digital Heart Rate, Alarms, Systole Sound, Blood Pressure/Pulse	1605
1606	ECG, Alarms, Systole Sound, Digital Display with Scan of Heart Rate, Blood Pressure/Pulse, Temperature	1607
1608	Telemetry ECG, Heart Rate, Alarms, Systole Sound	1609
1610	Telemetry ECG, Digital Heart Rate, Alarms, Systole Sound	1611

*Battery-operated units can be operated from line while recharging except 1700.

AO®

American Optical MEDICAL DIVISION, Bedford, MA 01730

Gentlemen:

☐ Please have a salesman call for an appointment to explain more about the AO 1600 Series and 1700 Portable Monitors.

Name _____ Title _____

Hospital _____

Address _____

City _____ State _____ Zip _____

Telephone _____

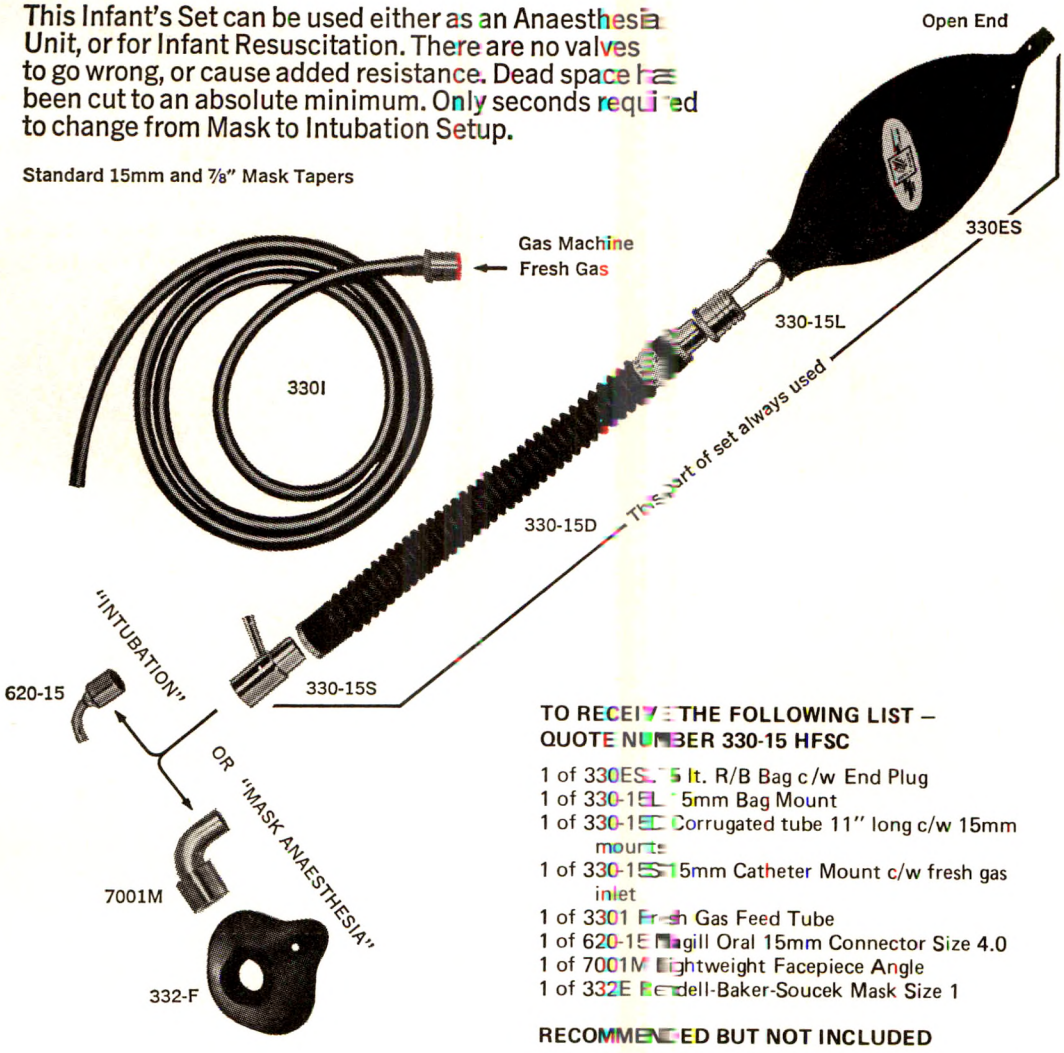
© American Optical Corporation, 1976 7954 Printed in USA 7/76

JACKSON-REES MODIFICATION OF AYRE'S T-PIECE

as used by leading children's hospitals

This Infant's Set can be used either as an Anaesthesia Unit, or for Infant Resuscitation. There are no valves to go wrong, or cause added resistance. Dead space has been cut to an absolute minimum. Only seconds required to change from Mask to Intubation Setup.

Standard 15mm and 7/8" Mask Tapers



TO RECEIVE THE FOLLOWING LIST – QUOTE NUMBER 330-15 HFSC

1 of 330ES 5 lt. R/B Bag c/w End Plug
1 of 330-15L 15mm Bag Mount
1 of 330-15C Corrugated tube 11" long c/w 15mm mounts
1 of 330-15S 15mm Catheter Mount c/w fresh gas inlet
1 of 3301 Fresh Gas Feed Tube
1 of 620-15 Magill Oral 15mm Connector Size 4.0
1 of 7001M Lightweight Facepiece Angle
1 of 332E Rendell-Baker-Soucek Mask Size 1

RECOMMENDED BUT NOT INCLUDED

6 (1 each) 330CF Foregger Coles Tubes 8 to 18 F.G.
1 No. 332F Rendell-Baker-Soucek Mask Size 2
1 No. 332L Rendell-Baker-Soucek Mask Size 3
1 330LC Leather Case
1 of 330-15D Corrugated tube c/w 15mm mounts.

We recommend you purchase a 330LC Leather Case to store this equipment — prevents loss or damage.

MIE

MEDICAL & INDUSTRIAL EQUIPMENT
A division of Claudius Ash Incorporated
655 - 73rd Street, Niagara Falls, New York 14304

SEND FOR COMPLETE LITERATURE

THE UNPROTECTED EYE THAT WAS "PROTECTED" WITH TAPE.

After tape removal, corneal damage is not evident on gross inspection.

After fluorescein staining, the green band delineates area of epithelial injury.

Corneal abrasion...the most common ocular complication of general anesthesia.[1,2] "It is painful, may progress to inflammation of the uveal tract, and in the presence of contamination may lead to a serious infection."[1]

This patient's eyes were taped shut and monitored throughout a surgical procedure that lasted several hours. No ocular lubricant was used.[3] The cause of the corneal abrasion is unknown...but it might have been prevented if Lacri-Lube® sterile ophthalmic ointment had been used as an added precaution before the tape was applied.

Lacri-Lube. The first sterile, nonmedicated ophthalmic ointment designed solely to lubricate the eye and protect it against the risk of chemical insult, dehydration, or corneal abrasion.

Whether you tape or not, make Lacri-Lube a part of your standard procedures to minimize the risks of general anesthesia.

LACRI-LUBE®
sterile ophthalmic ointment

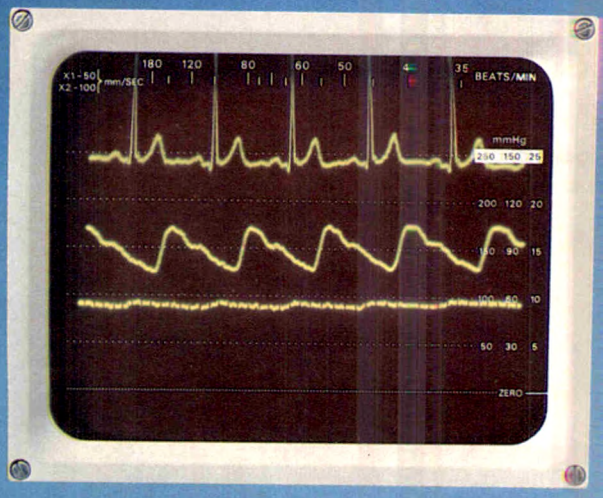
IT'S EXTRA INSURANCE.

References: 1. Snow, J.C. et al: Corneal Injuries During General Anesthesia, Anesthesia and Analgesia 54:465 (Jul-Aug) 1975. **2.** Terry, H.R. et al: Untoward Ophthalmic and Neurologic Events of Anesthesia, Surg Clin N Amer 45:927 1965. **3.** Data on file, Allergan Pharmaceuticals.

ALLERGAN Irvine, California/Pointe Claire, P.Q., Canada

© 1976 Allergan Pharmaceuticals

Only Tektronix gives you all three in a portable



ECG with One or Two Pressure Displays

Digital Readout of Vital Signs

Optional Recorder with Alphanumeric Printout

Tektronix' new 414 Single Pressure and 414FA Dual Pressure Monitors with hard copy recorder. Just compare for yourself: at $4200 and $4800 you won't find more capability in a portable instrument—and you won't find it in a more compact, easy-to-operate package. (Prices of the 414 and 414FA without recorders are only $2700 and $3200.)

Compare these features with any other monitor's:

- Two or three-trace crt display: ECG, arterial/venous, and the third trace arterial pressure channel
- Digital readout of heart rate, temperature, mean blood pressure, or alternating systolic/diastolic blood pressures
- Three selectable sweep speeds
- Heart rate and pulse pressure failure alarms
- Ac or battery operation
- Measures only 9.5 x 9.0 x 11.7 in. Weight: 18 lb.
- Recorder option providing single channel analog (printout) of ECG or pressure channels, plus alphanumeric printout of elapsed time, patient temperature, heart rate, systolic/diastolic and mean blood pressures

If you *really* compare, Tektronix Medical Products are

In a Class by Themselves

For more information, CALL TOLL FREE 800 547-4804 or write, Tektronix, Inc., P.O. Box 500, Beaverton, OR 97077.

U. S. sales price FOB Beaverton, Ore.

TEKTRONIX®
committed to technical excellence

Nesacaine®
(Chloroprocaine Hydrochloride)

1% and 2% solution in 30-ml. multiple-dose vials

For Infiltration and Regional Anesthesia

Nesacaine®-CE
(Chloroprocaine Hydrochloride)

2% and 3% solution in 30-ml. single-dose vials

For Caudal and Epidural Anesthesia

INDICATIONS

NESACAINE in multiple dose vials and NESACAINE-CE in single dose vials without preservatives are indicated for production of local anesthesia by infiltration injection and nerve block.*

*NESACAINE in multiple dose vials with preservatives is not to be used for caudal or epidural anesthesia. NESACAINE-CE contains no preservatives and the unused portion must be discarded after initial use.

CONTRAINDICATIONS

NESACAINE and NESACAINE-CE are contraindicated in patients hypersensitive to drugs of the PABA ester group. Central nervous system disease is generally considered a contraindication to caudal or epidural nerve block.

WARNINGS

RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE IMMEDIATELY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED. As NESACAINE-CE contains no preservative, discard unused drug remaining in vial after initial use. Equipment and drugs necessary for the treatment of inadvertent intravascular injection, intrathecal injection, or excessive dosage should be immediately available.

Usage in Pregnancy: Safe use of chloroprocaine hydrochloride has not been established with respect to adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential unless in the judgment of the physician the potential benefits outweigh the unknown hazards. In obstetrics, if vasoconstrictor drugs are used either to correct hypotension or are added to the local anesthetic solution, the obstetrician should be warned that some oxytocic drugs may cause severe persistent hypertension and even rupture of a cerebral blood vessel may occur during the post partum period.

Solutions containing vasoconstrictors, particularly epinephrine and norepinephrine, should be used with extreme caution in patients receiving certain antidepressants such as MAO inhibitors, and tricyclic compounds since a severe prolonged hypertension may occur.

PRECAUTIONS

The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious undesirable systemic side effects. Tolerance varies with the status of the patient. Debilitated patients, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical status.

Solutions containing vasoconstrictors should be used cautiously in the presence of disease which may adversely affect the patient's cardiovascular system.

Chloroprocaine hydrochloride should be employed cautiously in persons with known drug allergies or sensitivities.

The decision whether or not to use local anesthesia in the following conditions depends on the physician's appraisal of the advantages as opposed to the risk:

Paracervical block when fetal distress is anticipated or when predisposing factors causative of fetal distress are present (i.e., toxemia, prematurity, diabetes, etc.). Injection of solutions containing epinephrine in areas where the blood supply is limited (i.e., ears, nose, digits, etc.) or when peripheral vascular disease is present.

ADVERSE REACTIONS

Adverse reactions result from high plasma levels due to rapid absorption, inadvertent intravascular injection or excessive dosage. Hypersensitivity, idiosyncrasy, or diminished tolerance are other causes of reactions. Reactions due to overdosage (high plasma levels) are systemic and involve the central nervous system and the cardiovascular system.

Reactions involving the central nervous system are characterized by excitation and/or depression. Nervousness, dizziness, blurred vision or tremors may occur followed by drowsiness, convulsions, unconsciousness and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestations may be drowsiness merging into unconsciousness and respiratory arrest.

Reactions involving the cardiovascular system include depression of the myocardium, hypotension, bradycardia and even cardiac arrest.

Treatment of a patient with toxic manifestations consists of maintaining an airway, and supporting ventilation using oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system consists of using vasopressors, preferably those that stimulate the myocardium (e.g., ephedrine) and intravenous administration in small increments of an ultrashort acting barbiturate (i.e., thiopental, thiamylal) or a short acting barbiturate if these are not available (secobarbital, pentobarbital) or a short acting muscle relaxant (succinylcholine), together with oxygen. Muscle relaxants and intravenous barbiturates should be used only by those familiar with their use.

Allergic reactions are characterized by cutaneous lesions, urticaria, edema and other manifestations of allergy. The detection of sensitivity by skin testing is of doubtful value.

DOSAGE AND ADMINISTRATION

The maximum single recommended doses of chloroprocaine hydrochloride are: without epinephrine, 800 mg.; with epinephrine (1:200,000), 1000 mg. The recommended dosage is based on requirements for the average adult and should be reduced for elderly or debilitated patients and children.

The recommended doses given below serve only as a guide to the amount of anesthetic required for most routine procedures.

1. INFILTRATION AND NERVE BLOCK (NESACAINE)

Type of Block	Volume	Concentration
Occipital	3-5 ml.	1%-2%
Mandibular	2-3 ml.	2%
Maxillary	2-3 ml.	2%
Infra-orbital	0.5-1 ml.	2%
Cervical	3-4 ml. (for each segment)	1%-2%
Brachial plexus	30-40 ml.	2%
Ulnar nerve	3-5 ml.	2%
Paravertebral	3-5 ml.	2%
Intercostal	3 ml.	1%-2%
Sciatic nerve	10-15 ml.	2%
Stellate ganglion	5-10 ml.	1%-2%
Lumbar sympathetic (1 needle technic)	15-20 ml.	1%-2%
Interdigital	3-4 ml. (without epinephrine)	1%-2%

Fractional doses, up to 300 to 600 mg., may be given at 50 minute intervals.

2. CAUDAL AND EPIDURAL BLOCK (NESACAINE-CE)

For *caudal anesthesia* the initial dose is 15 to 25 ml. of a 2% or 3% solution. Repeated doses may be given at 40 to 60 minute intervals.

For *epidural anesthesia* in the lumbar and sacral regions 2.0 to 2.5 ml. per segment of a 2% or 3% solution can be used. The usual total volume of Nesacaine-CE is from 15 to 25 ml. Repeated doses 2 to 6 ml. less than the original dose may be given at 40 to 50 minute intervals.

HOW SUPPLIED

Nesacaine is supplied as follows:

1% solution (10 mg/ml.) in 30 ml. multiple-dose vials, 12 vials per carton.

2% solution (20 mg/ml.) in 30 ml. multiple-dose vials, 12 vials per carton.

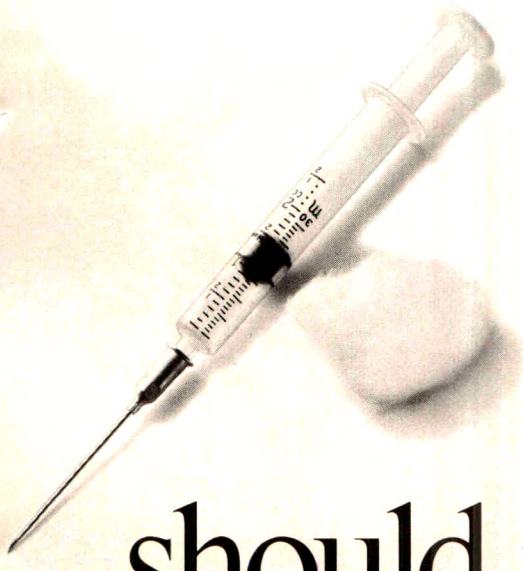
Nesacaine-CE is supplied as follows:

2% solution (20 mg/ml.) in 30 ml. single-dose vials, 12 vials per carton.

3% solution (30 mg/ml.) in 30 ml. single-dose vials, 12 vials per carton.

PENNWALT

Pennwalt Prescription Products
Pharmaceutical Division
Pennwalt Corporation
Rochester, New York 14603



A local anesthetic should meet your needs...

Rapid Onset of Action. Saves doctor, nurse and patient time.

Effective Anesthesia. Nesacaine (Chloroprocaine Hydrochloride) offers 80% to 90% pain-free procedures at recommended doses.

Exceptional Safety. Less potential for postoperative complications. Nesacaine is rapidly hydrolized in plasma, whereas lidocaine and other amide-type local anesthetics are metabolized in the liver. With Nesacaine, therefore, there is minimal potential risk of systemic toxicity, accumulation of metabolites, stimulation of CNS or cardiovascular effects.

Excellent Penetration. Chloroprocaine's lipid solubility and ionization characteristics impart it with excellent penetration.

Minimal Irritation at Injection Site. Few patient complaints about procedural pain, little soreness and inflammation after procedure.

Rapid and Complete Wear-Off. No residual numbness, patient back to normal faster.

See opposite page for brief prescribing information.

Look into

Nesacaine®

(Chloroprocaine Hydrochloride)

It meets your needs.

Documented Compatibility
with Epinephrine
Ethra

Unlike some anesthetic agents, ETHRANE® (enflurane) does not significantly increase myocardial sensitivity to exogenous epinephrine.*[1-4] Thus ETHRANE allows an adequate margin of safety during anesthesia when epinephrine is used under the conditions prescribed for local hemostasis—with or without concomitant use of lidocaine.*[1-4] Of course, all customary precautions in the use of vasoconstrictor substances should be observed.

Similarly, reported data has also supported the use of ETHRANE anesthesia in the resection of a pheochromocytoma without significant increase in myocardial sensitivity to endogenous catecholamines.[5-7]

ETHRANE anesthesia also ensures: fast induction, quick recovery, maintenance of cardiac rhythm, excellent muscle relaxation, and few aftereffects.[8]

These advantages of ETHRANE—plus its compatibility with subcutaneously administered epinephrine—demonstrate its versatility in concept and performance.

WARNING: Motor activity exemplified by movement of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia. For additional warnings, contraindications, and precautions, see following page.

ne® (enflurane)

Please see following page for summary of product information.

1. Johnston, R. R., et al.: A comparative interaction of epinephrine with enflurane, isoflurane, and halothane in man: Epinephrine induced PVC's and anesthesia. Anes & Analg, Sept/Oct, 1976.
2. Reisner, L. S., Lippmann, M.: Ventricular arrhythmias after epinephrine injection in enflurane and in halothane anesthesia. Anesth & Analg **54**:468-470, 1975.
3. Lippmann, M., Reisner, L. S.: Epinephrine injection with enflurane anesthesia: Incidence of cardiac arrhythmias. Anesth & Analg **53**:868-889, 1974.
4. Konchigeri, H. N., et al.: Effect of epinephrine during enflurane anesthesia. Anesth & Analg **53**:894-897, 1974.
5. Kreul, J. F., et al.: Hemodynamic and catecholamine studies during pheochromocytoma resection under enflurane anesthesia. Anesthesiology **44**:265-268, 1976.
6. Ortiz, F. T., Diaz, P. M.: Use of enflurane for pheochromocytoma removal. Anesthesiology **42**:495-497, 1975.
7. Koorniva, C. J., Eltringham, R.: The use of enflurane during resection of a pheochromocytoma. Anesthesiology **41**:399-400, 1974.
8. Additional data on file, Medical Department, Ohio Medical Products.

Ohio Medical Products
3030 AIRCO DRIVE
MADISON, WISCONSIN 53701

AIRCO®

Ethrane® (enflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription

DESCRIPTION

ETHRANE (enflurane) is a nonflammable anesthetic agent. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether, and its structural formula is:

Some physical constants of the compound are:

Molecular weight		184.5
Boiling point 760 mm Hg.		56.5°C
Refractive index n_D^{20}		1.3026-1.3030
Specific gravity 25°/25°C		1.517
Vapor pressure in mm Hg.**	20°C	174.5
	25°C	217.7
	36°C	345.2

**Equation for calculation of enflurane vapor pressures:

$\log_{10} P = A + \frac{B}{T}$

A = 7.967
B = −1678.4
T = °C + 273.16 (Kelvin)

Partition coefficients @ 37°C	
Water-gas	0.82
Blood-gas	1.91
Oil-gas	98.5
Partition coefficients @ 25°C-rubber and plastic	
Conductive rubber	74.0
Butyl rubber	90.0
Polyvinylchloride	120.0
Polyethylene	∼2.0
Polyurethane	∼1.5
Polyolefin	∼1.2
Butyl acetate	∼3.0
Solubility of enflurane in H_2O at 22°C	0.275%
Solubility of H_2O in enflurane	0.13%
Purity by gas chromatography	>99.9%
Flammability in air	None
Flammability in oxygen (Entire concentration range to saturation at 71 and 113°F and 743 mm Hg. pressure.)	None
M.A.C. (Minimum alveolar concentration)	
Man with pure oxygen	1.68
Man with 70% nitrous oxide	0.56 (est.)

ETHRANE is a clear, colorless, stable liquid without added chemical stabilizers. ETHRANE has a mild, sweet odor. Storage of samples in indirect sunlight in clear, colorless glass for a five year period, as well as direct exposure for 30 hours to a 2 amp, 115 V., 60 cycle long wave U.V. light, produced no changes in composition detectable by gas chromatography. ETHRANE in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed none of the alkali, indicative of strong base stability. ETHRANE does not decompose in contact with soda lime. ETHRANE does not attack aluminum, tin, brass, iron or copper.

ACTIONS

ETHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ETHRANE are rapid. ETHRANE does not appear to stimulate excess salivation or tracheobronchial secretions, or affect bronchomotor tone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ETHRANE. ETHRANE reduces ventilation as depth of anesthesia increases. ETHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

While ETHRANE has been shown to sensitize the myocardial conduction system to epinephrine in the dog and may produce serious arrhythmias, studies in cats and man indicate considerable margin of safety in the administration of epinephrine containing solutions during ETHRANE anesthesia. ETHRANE anesthesia has been used in medical conditions involving high levels of endogenous catecholamines, as well as surgical procedures involving carefully administered quantities of epinephrine containing solutions. On the basis of this experience, up to 10 ml. of 1:100,000 or 1:200,000 epinephrine containing solution alone or in conjunction with local anesthetics may be injected subcutaneously at a rate of not more than 10 ml. per minute and no more than 30 ml. per hour. More dilute solutions and reduced dosages should be used in highly vascular areas. All customary precautions in the use of vasoconstrictor substances should be observed.

Muscle relaxation is adequate for intra-abdominal operation at normal levels of anesthesia. Should greater relaxation be necessary, minimal doses of muscle relaxants may be used. All commonly used muscle relaxants are compatible with ETHRANE. **THE NONDEPOLARIZING MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED.** Neostigmine does not reverse the direct effect of ETHRANE.

Biotransformation of ETHRANE in man results in low levels of serum fluoride ions averaging 15 mM/L. These levels are well below the 50 mM/L seen to produce renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation.

INDICATIONS

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.

WARNINGS

Increasing depth of anesthesia with ETHRANE (enflurane) produces a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by hyperventilation producing low arterial carbon dioxide tension. The pattern serves as a warning that depth of anesthesia is excessive. Cerebral blood flow and metabolism studies in normal volunteers during seizure patterns show no evidence of cerebral hypoxia, and recovery appears to be uncomplicated.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. With deep levels of anesthesia, more marked hypotension and respiratory depression are encountered.

The action of nondepolarizing relaxants is augmented by ETHRANE. Less than the usual amounts of these drugs should be used. The time for recovery from the myoneural effect of these relaxants is greater in the presence of ETHRANE than for other commonly used anesthetics.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

PRECAUTIONS

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ETHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ETHRANE.

ADVERSE REACTIONS

1. Motor activity exemplified by movement of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia.
2. Hypotension and respiratory depression have been reported.
3. Arrhythmias, shivering, nausea, and vomiting have been reported.
4. Elevation of the white blood count has been observed. It has not been determined whether this is related to ETHRANE or to surgical stress.

DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ETHRANE;
b) vaporizers from which delivered flows can easily and readily be calculated.

Maintenance concentration should not exceed 3%. Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ETHRANE and the heart rate remains constant. The use of anticholinergic drugs is a matter of choice.

Induction: Induction may be achieved using ETHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ETHRANE mixture. In general, inspired concentrations of 3.5-4.5% ETHRANE produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be attained with 1.5-3.0% concentration. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm range is preferred to hyper- or hypoventilation in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ETHRANE concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration; establish that the airway is clear and initiate assisted or controlled ventilation with pure oxygen as circumstances dictate.

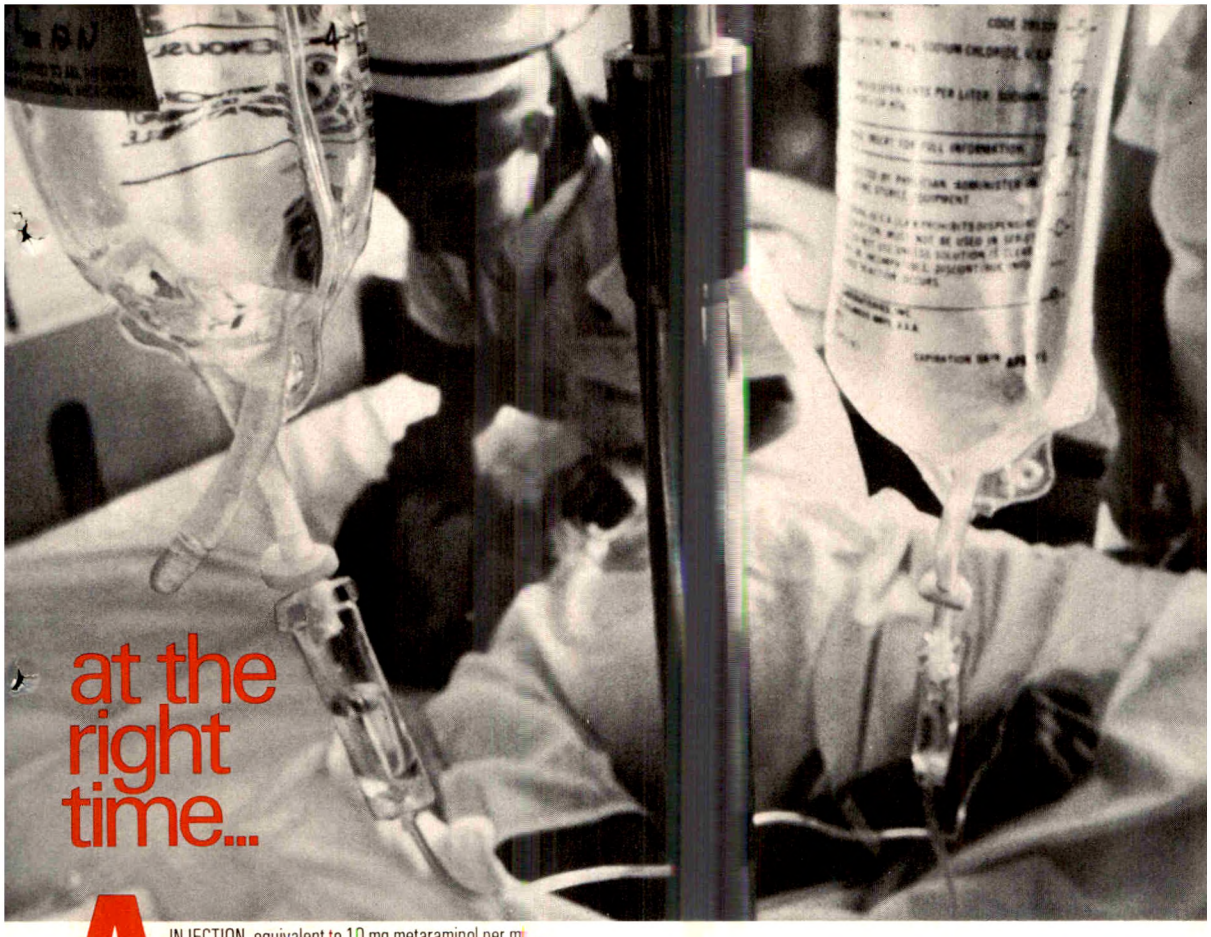
ADMINISTRATION EQUIPMENT

ETHRANE (enflurane) may be administered from a flow-through type vaporizer manufactured and specifically calibrated for ETHRANE. Vaporizers which deliver saturated vapor at reasonable flows but are not specifically calibrated for ETHRANE may be used. A reasonably accurate estimation of delivered ETHRANE concentration may be made by use of the nomograph on the reverse side.

ETHRANE contains no stabilizer. Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

PACKAGING

ETHRANE (enflurane) is packaged in 125 and 250 ml. amber bottles. No additives or stabilizers are present.



INJECTION, equivalent to 10 mg metaraminol per ml

Aramine® (Metaraminol Bitartrate | MSD)

a vasopressor with positive inotropic effect

Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:
Effective: ARAMINE is indicated for prevention and treatment of the acute hypotensive state occurring with spinal anesthesia. Adjunctive treatment of hypotension due to hemorrhage; reactions to medications; surgical complications; and shock associated with brain damage due to trauma or tumor.
"Probably" effective: It may also be useful as an adjunct in the treatment of hypotension due to cardiogenic shock or septicemia.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Use should be avoided with cyclopropane or halothane anesthesia, unless clinical circumstances demand such use.

Precautions: Use with caution to avoid excessive blood pressure response. Rapidly induced hypertensive responses have been reported to cause acute pulmonary edema, arrhythmias, and cardiac arrest. Use with caution in digitalized patients, since the combination of digitalis and sympathomimetic amines is capable of causing ectopic arrhythmic activity. Treat cirrhotic patients cautiously; if diuresis ensues, restore electrolytes. Fatal ventricular arrhythmia has been reported in one patient with Laennec's cirrhosis. In several instances, ventricular extrasystoles that appeared during infusion have subsided promptly on reduction of infusion rate. Since metaraminol has prolonged duration of action, a cumulative effect is possible, leading to prolonged elevation of blood pressure even with discontinuation of therapy. Monoamine oxidase inhibitors have been reported to potentiate action of sympathomimetic amines.
When vasopressor amines are used for long periods resulting volume and may cause perpetuation of the shock state. Plasma volume may be reduced in all types of shock, and measurement of central venous pressure is the most useful means of assessing the adequacy of the circulating blood volume; blood or plasma volume expanders should be employed for hypotension or shock due mainly to decreased circulating volume. Because of its vasoconstrictor effect, metaraminol should be used with caution in heart or thyroid disease, hypertension, or diabetes. Sympathomimetic amines may provoke relapse in patients with history of malaria.

Adverse Reactions: Sinus or ventricular tachycardia, or other arrhythmias, especially in patients with myocardial infarction. Abscess formation, tissue necrosis, or sloughing may rarely follow use. In choosing the site of injection, it is important to avoid those areas recognized as *not* suitable for use of any pressor agent, and to discontinue infusion immediately if infiltration or thrombosis occurs. The larger veins of the antecubital fossa or the thigh are preferred to veins in the dorsum of the hand or ankle veins, particularly in patients with peripheral vascular disease, diabetes mellitus, Buerger's disease, or conditions with coexistent hypercoagulability.

Note: Response to vasopressors may be poor in patients with coexistent shock and acidosis. Established methods of shock management, such as blood or fluid replacement when indicated, and other measures directed to the specific cause of the shock state also should be used. *Only Sodium Chloride Injection or 5 percent Dextrose Injection should be used as a diluent.*

How Supplied: Injection, in 1-ml ampuls and 10-ml vials, containing per ml: metaraminol bitartrate equivalent to 10.0 mg metaraminol; inactive ingredients: sodium chloride, 4.4 mg; water for injection, q.s. ad 1.0 ml; and 0.15% methylparaben, 0.02% propylparaben and 0.2% sodium bisulfite added as preservatives.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division

MSD
MERCK SHARP&

The local that gives you the longest anesthesia gives your patient longer postoperative analgesia.

Marcaine® hydrochloride (brand of bupivacaine hydrochloride)—available with or without epinephrine—is the local anesthetic that provides the longest duration of action among commonly used local anesthetics. Which minimizes the problems of "continuous" technique or repeat doses.

Marcaine also provides longer postoperative analgesia. Which reduces the need for postoperative narcotics.

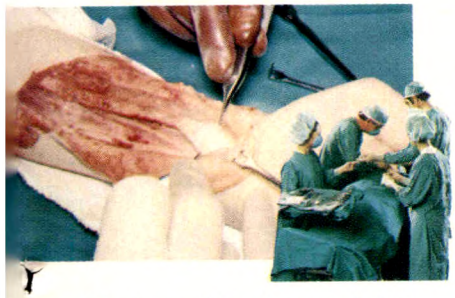
And in data in over 3,000 patients, Marcaine was reported to have excellent or satisfactory results in more than 96% of cases.

Extended anesthesia for the surgeon

In regional blocks, Marcaine, with or without epinephrine, usually provides anesthesia at least 1½ to 2 times longer than lidocaine or mepivacaine. And approximately 20% longer than tetracaine.

In fact, anesthesia may extend up to 9 hours for peridural block and up to 12 hours for peripheral nerve block. This has been established in several thousand surgical and obstetrical patients.[1-4]

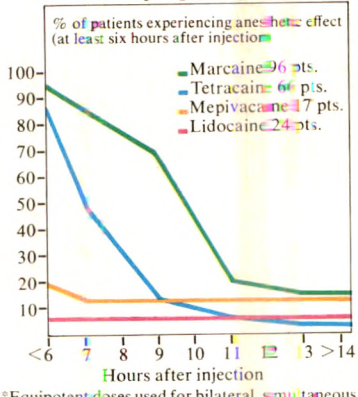
In fact, a single Marcaine epidural injection, with or without epinephrine, may be enough for up to 3½[4] or more[5] hours of anesthesia for surgery, and often provides analgesia that carries over into the recovery room and beyond. When necessary, doses may be repeated up to once every three hours. Caution is advised in administration of repeat doses to patients with severe liver disease. Until further experience is gained, total daily dose of



400 mg. should not be exceeded nor is administration to children under 12 recommended. Also see epinephrine warnings and precautions statements on next page.

This longer anesthetic action can minimize problems of "continuous" technique or repeat doses. Thus, there is the further advantage of a reduced likelihood of introducing infection since injections are less frequent.[6]

Chart I
Duration of anesthesia
Percentage of patients experiencing anesthetic effect–
Comparison of Marcaine with epinephrine and other local anesthetic/epinephrine preparations*



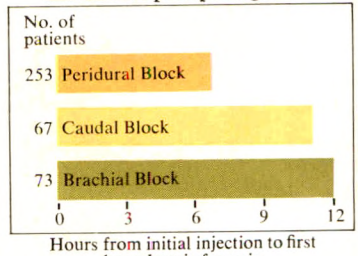
*Equipotent doses used for bilateral, simultaneous blocks of sciatic/femoral, intercostal, or brachial/axillary nerves. Adapted from Moore, D. C.: Data in the files of the Sterling-Winthrop Research Institute.

Extended postoperative analgesia for the patient

Marcaine, with or without epinephrine, gives your patient more—considerably more—postanesthetic analgesia than other local anesthetics in various types of nerve block.[3,4,7,8] An analgesia that persists after the return of motor function and even cutaneous sensation.[7] As a result, you may be able to defer[1,5] and sometimes even eliminate,[5] postoperative narcotics. Chart II illustrates the average duration of time between the initial Marcaine injection and the need for postop analgesics. Many of the 67 patients given Marcaine with or without epinephrine, caudally for rectal surgery did not complain of pain for 11 hours or longer following induction.

In another group of 40 patients[8] given Marcaine or mepivacaine, both with epinephrine, locally for tonsillectomy, Marcaine pain relief lasted 3 to 5 times longer than that provided by mepivacaine. And in a study[1] of 65 patients given 0.5% Marcaine with epinephrine caudally for rectal or other perineal surgery, complete sensation returned in a mean of 8½ hours for the average patient. And the majority of these patients did not require a narcotic for an additional 1 to 3 hours.

Chart II
Duration of time between injection of Marcaine, with or without epinephrine, and need for postop analgesics†



†Average—exclusion of extremes and failures. Adapted from Lund, P.C., *et al.*: *Anesth. Analg.* 49:103, Jan.-Feb. 1970.

Excellent clinical acceptance

Marcaine, with or without epinephrine, was administered to 3,112 patients for various types of local anesthesia.[9] Of these patients, only 2 experienced a systemic reaction. Although Marcaine has a very wide safety margin, adverse reactions characteristic of those associated with other amide local anesthetics may occur.

Marcaine is indicated for most anesthetic blocks; however, until further clinical experience is gained paracervical block is not recommended.

See important product information concerning warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations on next page.

Extends the limits of time in anesthesia[1-4]
Extends the limits of time in postoperative analgesia[3,4,7,8]

Marcaine® hydrochloride

Brand of
bupivacaine hydrochloride

with or without epinephrine 1:200,000

Winthrop

MARCAINE® Hydrochloride
Brand of **bupivacaine hydrochloride**

Indications: Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

Contraindication: Marcaine is contraindicated in patients with known hypersensitivity to it.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. Reproduction studies have been performed in rats and rabbits and there is no evidence of harm to the animal fetus. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions: The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Adverse Reactions: Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings).

Allergic reactions, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

References: 1. Moore, D. C., Bridenbaugh, L. D., Bridenbaugh, P. O., *et al.*: Bupivacaine, a review of 2,077 cases, *J.A.M.A. 214*:713, Oct. 26, 1970. **2.** Moore, D. C., Bridenbaugh, L. D., Bridenbaugh, P. O., *et al.*: Bupivacaine for peripheral nerve block: a comparison with mepivacaine, lidocaine and tetracaine, *Anesthesiology 32*:460, May 1970. **3.** Hollman, A.: Axillary plexus block: a double-blind study of 59 cases using mepivacaine and LAC-43, *Acta Anaesthesiol. Scand., Suppl. 21*:53, 1966. **4.** Bromage, P. R.: A comparison of bupivacaine and tetracaine in epidural anesthesia for surgery, *Can. Anaesth. Soc. J. 16*:37, Jan. 1969. **5.** Lund, P. C., Cwik, J. C., and Vallesteros, F.: Bupivacaine—a new long-acting local anesthetic agent, a preliminary clinical and laboratory report, *Anesth. Analg. 49*:103, Jan.-Feb. 1970. **6.** Wise, G. F.: Guest Discussions, *Anesth. Analg. 49*:113, Jan.-Feb. 1970. **7.** Moore, D. C.: Data in the files of the Sterling-Winthrop Research Institute. **8.** Puento-Egido, J. J., Dudeck, J., and Nolte, H.: The clinical use of the local anesthetic agent Marcaine (Carbostesin®), *Anaesthesist 16*:224, August 1967. **9.** Data in the files of the Sterling-Winthrop Research Institute.

(1664MB)

Winthrop

Winthrop Laboratories, New York, N.Y. 10016

FORMULA

PRODUCT IDENTIFICATION			MULTIPLE DOSE VIAL						SINGLE DOSE AMPUL				
Marcaine HCl (brand of bupivacaine HCl)		Epinephrine* (as bitartrate)	Methylparaben	Sodium Bisulfite	Thioglycerol	Ascorbic Acid	60% Sod. Lactate	Edetate Calcium Disodium	Sodium Bisulfite	Thioglycerol	Ascorbic Acid	60% Sod. Lactate	Edetate Calcium Disodium
%	mg./ml.	Dilution	mg./ml.	mg./ml.	ml./ml.	mg./ml.	ml./ml.	mg./ml.	mg./ml.	ml./ml.	mg./ml.	ml./ml.	mg./ml.
0.25	2.5	—	1	—	—	—	—	—	—	—	—	—	—
0.25	2.5	1:200,000	1	0.5	.001	2	.0017	0.1	.5	.001	2	.0017	0.1
0.5	5.0	—	1	—	—	—	—	—	—	—	—	—	—
0.5	5.0	1:200,000	1	0.5	.001	2	.0017	0.1	.5	.001	2	.0017	0.1
0.75	7.5	—	Not Available in Vials						—	—	—	—	—
0.75	7.5	1:200,000							.5	.001	2	.0017	0.1

Note: The pH of these solutions is adjusted with sodium hydroxide or hydrochloric acid. Sodium chloride has been added to make each solution isotonic.

*Solutions of Marcaine that contain epinephrine should not be autoclaved.

Federal law prohibits dispensing without a prescription.

Extends the limits of time in anesthesia[1-4]
Extends the limits of time in postoperative analgesia[3,4,7,8]

Marcaine® hydrochloride

Brand of
bupivacaine hydrochloride

with or without epinephrine 1:200,000

NARKOMED

TOTAL ANESTHESIA SYSTEM

NARKOMED, a refreshing new concept in anesthesia machine design and styling, incorporating a contemporary anesthesia dispensing system with a built-in fluidic anesthesia ventilator and the widest variety of options.

Please return the accompanying coupon for further information.

NORTH AMERICAN DRÄGER

NORTH AMERICAN DRÄGER

P.O. Box 121
Telford, Pa. 18969

____ Please send information on the NARKOMED TOTAL ANESTHESIA SYSTEM
____ Please include a copy of Anesthesia Accessories Catalog
____ Please send information on _____

NAME _____

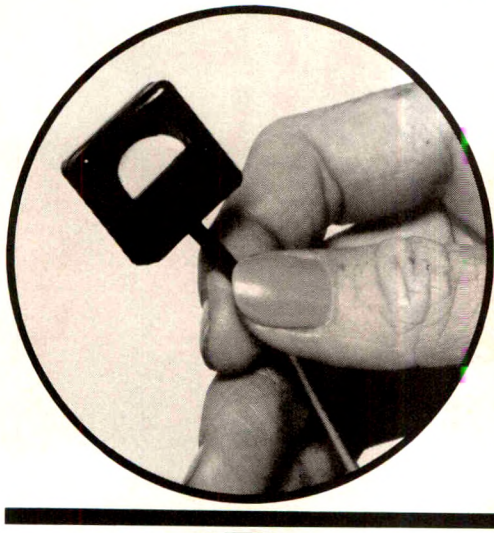
TITLE _____

HOSPITAL _____

ADDRESS _____

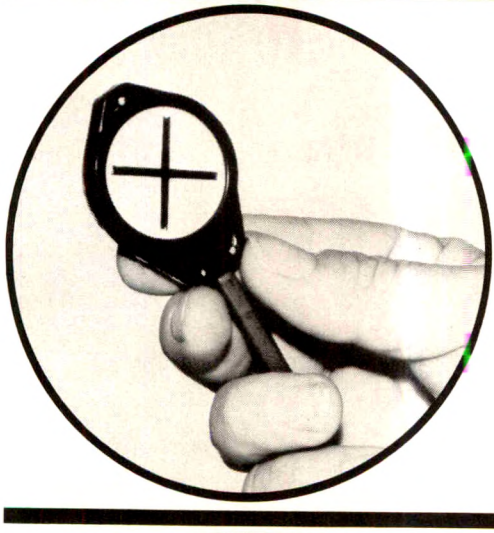
STATE ZIP

VERSATONE® MULTI-PURPOSE DOPPLER INSTRUMENT



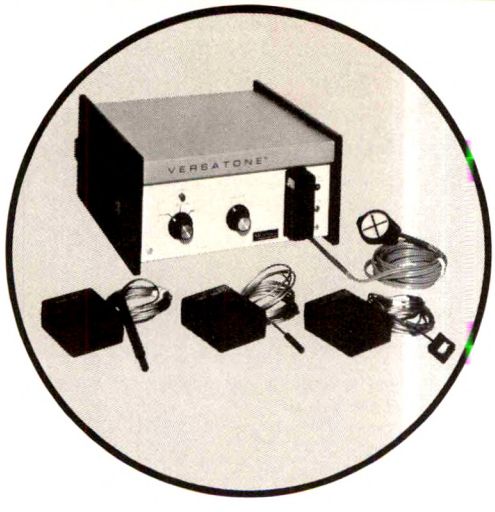
FOR MONITORING DOPPLER SOUNDS OF BLOOD FLOW AND TO TAKE DOPPLER SYSTOLIC BLOOD PRESSURE

This sensitive Doppler probe is easy to tape in position for non-invasive detection and monitoring of arterial blood flow during surgery. Used with an occlusive cuff and manometer, systolic blood pressures may be obtained even on infants and hypotensive patients.



FOR EARLY DETECTION OF VENOUS AIR EMBOLISM

This sensitive wide-angle Doppler probe is particularly well suited for the detection of venous air emboli which may occur during neurosurgical procedures performed with the patient in the upright position. It also detects motion of the heart muscle, heart valves and blood flow.

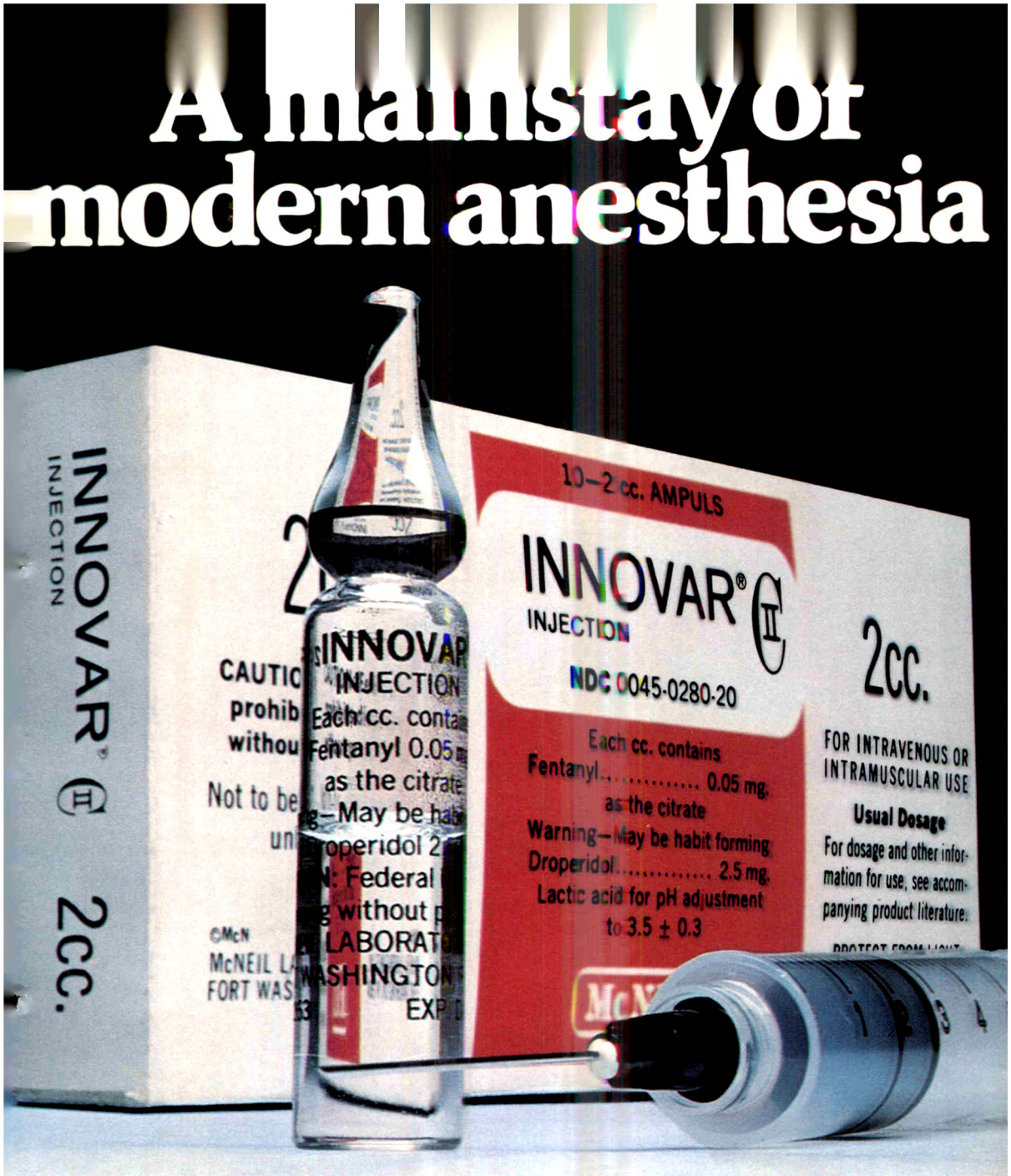


VERSATONE D8 DOPPLER

The Model D8 VERSATONE Doppler instrument is designed to use interchangeable probes of various frequencies and configurations. It is powered by a rechargeable battery and has a built-in loudspeaker. Options include an electrocautery sensor and cut-out, a molded earset for private listening, and a chart recording circuit. The two probes shown above are particularly useful to the anesthesiologist. Two sizes of pencil shaped probes are also available. These are useful for intraoperative assessment of flow in exposed vessels, as well as for transcutaneous flow detection.

MED SONICS
For more information call or write:
P.O. Box M (340 Pioneer Way) Mountain View, CA (415) 965-3333

A mainstay of modern anesthesia



- As an adjunct to general anesthesia
- As a supplement to regional anesthesia
- Used without a general anesthetic in certain diagnostic procedures

INNOVAR® injection is available for use only upon direction of a physician.

Special educational material available

A Programmed Instruction Manual on the chemistry, pharmacology and clinical applications of INNOVAR injection and its components is available from McNeil Laboratories. For further information, please write: Product Director, INNOVAR injection, McNeil Laboratories, Inc., Fort Washington, Pa. 19034.

© McN 1975

For prescribing information including Contraindications, Warnings, Precautions and Adverse Reactions, please turn page.

Innovar® injection

The two components of INNOVAR® injection, fentanyl and droperidol, have different pharmacologic actions. Before administering INNOVAR injection, the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action.

DESCRIPTION

Each cc. contains (in a 1:50 ratio):

Fentanyl ..... 0.05 mg.
as the citrate

Warning: May be habit forming

Droperidol ..... 2.5 mg.
Lactic acid for adjustment of pH to 3.5± 0.3

FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY

Protect from Light

ACTIONS INNOVAR injection is a combination drug containing a narcotic analgesic, fentanyl, and a neuroleptic (major tranquilizer), droperidol. The combined effect, sometimes referred to as neuroleptanalgesia, is characterized by general quiescence, reduced motor activity, and profound analgesia; complete loss of consciousness usually does not occur from use of INNOVAR injection alone. The incidence of early postoperative pain and emesis may be reduced.

A. Fentanyl is a narcotic analgesic with actions qualitatively similar to those of morphine and meperidine. Fentanyl in a dose of 0.1 mg. (2.0 cc.) is approximately equivalent in analgesic activity to 10 mg. of morphine or 75 mg. of meperidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. Fentanyl appears to have less emetic activity than other narcotic analgesics. Histamine assays, and skin wheal testing in man, as well as *in vivo* testing in dogs indicate that histamine release rarely occurs with fentanyl.

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. It may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia, and bronchoconstriction.

The onset of action of fentanyl is almost immediate when the drug is given intravenously; however, maximal analgesic and respiratory depressant effect may not be noted for several minutes. The average duration of action of the analgesic effect is 30 to 60 minutes. Following intramuscular administration, the onset of action is from seven to eight minutes, and the duration of action is from one to two hours. Although the duration of the respiratory depressant effect is unknown, as with other narcotic analgesics, it may be considerably longer than the analgesic effect.

B. Droperidol produces marked tranquilization and sedation. It also produces an antiemetic effect as evidenced by the antagonism of apomorphine in dogs. It potentiates other CNS depressants. It also produces mild alpha adrenergic blockade, peripheral vascular dilatation and reduction of the pressor effect of epinephrine. Droperidol can produce hypotension and decreased peripheral vascular resistance. It may decrease pulmonary arterial pressure (particularly if it is abnormally high). It may reduce the incidence of epinephrine-induced arrhythmias but it does not prevent other cardiac arrhythmias. The onset of action is from three to ten minutes following intravenous or intramuscular administration. The full effect, however, may not be apparent for 30 minutes. The duration of the sedative and tranquilizing effects generally is two to four hours. Alteration of consciousness may persist as long as 12 hours. This is in contrast to the much shorter duration of action of fentanyl.

INDICATIONS INNOVAR injection is indicated to produce tranquilization and analgesia for surgical and diagnostic procedures. It may be used as an anesthetic premedication, for the induction of anesthesia, and as an adjunct in the maintenance of general and regional anesthesia. If the supplementation of analgesia is necessary, SUBLIMAZE® (fentanyl) injection alone rather than the combination drug INNOVAR injection should usually be used.

CONTRAINDICATIONS INNOVAR injection should not be used in patients who are hypersensitive to either component.

WARNINGS PATIENTS WHO HAVE RECEIVED *INNOVAR* INJECTION SHOULD BE UNDER APPROPRIATE SURVEILLANCE.

RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INNOVAR injection, the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses, as low as 1/4 to 1/3 those usually recommended.

INNOVAR injection may cause muscle rigidity, particularly involving the muscles of respiration. This effect is due to the fentanyl component and is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs it is managed by the use of assisted or controlled respiration and by a neuromuscular blocking drug, if necessary.

FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD ALSO BE AVAILABLE.

Drug Dependence: *Fentanyl, the narcotic analgesic component, can produce drug dependence of the morphine type and therefore has the potential for being abused.*

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl, in this regard, has not been established, the use of INNOVAR injection or SUBLIMAZE fentanyl in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure: INNOVAR injection should be used with caution in patients who may be particularly susceptible to respiratory depression such as comatose patients who may have a head injury or brain tumor. In addition, these drugs may obscure the clinical course of patients with head injury.

Usage in Children: The safety of INNOVAR injection in children two years of age or younger has not been established.

Usage in Pregnancy: The safe use of INNOVAR injection has not been established with respect to possible adverse effects upon fetal development.

Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS *The initial dose of INNOVAR injection should be appropriately reduced in elderly, debilitated and other poor risk patients. The effect of the initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves, and can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms (see Actions) fentanyl and droperidol also depress respiration and blood pressure. Therefore, when INNOVAR injection is used to supplement these forms of anesthesia, the anesthetist must be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

The droperidol component of INNOVAR injection may decrease pulmonary arterial pressure. This fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient.

Vital signs should be monitored routinely.

INNOVAR injection, and SUBLIMAZE fentanyl, should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised ventilation. In such patients narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia this can be managed by assisted or controlled respiration. Postoperatively respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists (levallorphan, nalorphine, and naloxone); consult individual prescribing information before using.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INNOVAR injection. When patients have received such drugs, the dose of INNOVAR injection required will be less than usual. Likewise, following the administration of INNOVAR injection the dose of other CNS depressant drugs should be reduced.

INNOVAR injection should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in the moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus these other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INNOVAR injection due to the alpha-adrenergic blocking action of droperidol.

The fentanyl component may produce bradycardia, which may be treated with atropine; however, INNOVAR injection should be used with caution in patients with cardiac bradyarrhythmias.

When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

ADVERSE REACTIONS The most common serious adverse reactions reported to occur with INNOVAR injection are respiratory depression, apnea, muscular rigidity, and hypotension; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, twitching, blurred vision, hyperactivity on induction, laryngospasm, transient hypertension, nausea and emesis, diaphoresis, emergence delirium, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).

Postoperative drowsiness is also frequently reported.

OVERDOSAGE ***Manifestations:*** The manifestations of INNOVAR injection overdosage are an extension of its pharmacologic actions.

Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered. A specific narcotic antagonist such as nalorphine, levallorphan or naloxone should be available for use as indicated to manage respiratory depression caused by the narcotic component fentanyl. This does not preclude the use of more immediate countermeasures. Consult the package inserts for the individual narcotic antagonists for details about use.

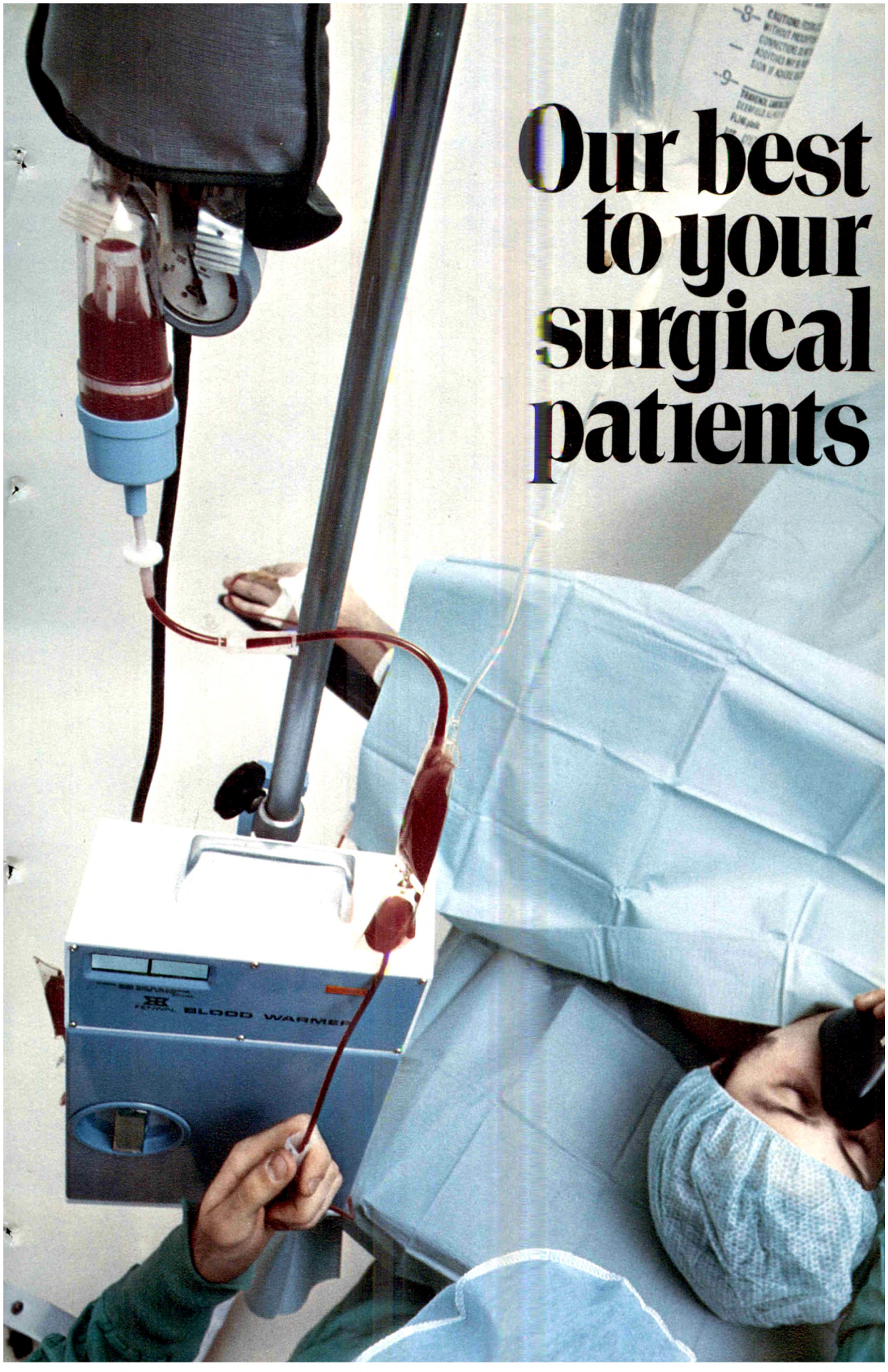
HOW SUPPLIED INNOVAR® injection is supplied in 2 cc. (**NDC** 0045-0280-20) and 5 cc. (**NDC** 0045-0280-50) ampuls, in packages of 10.

IMPORTANT: Complete dosage information is available in insert which accompanies each package (or on request). The drug is available only upon direction of a physician.

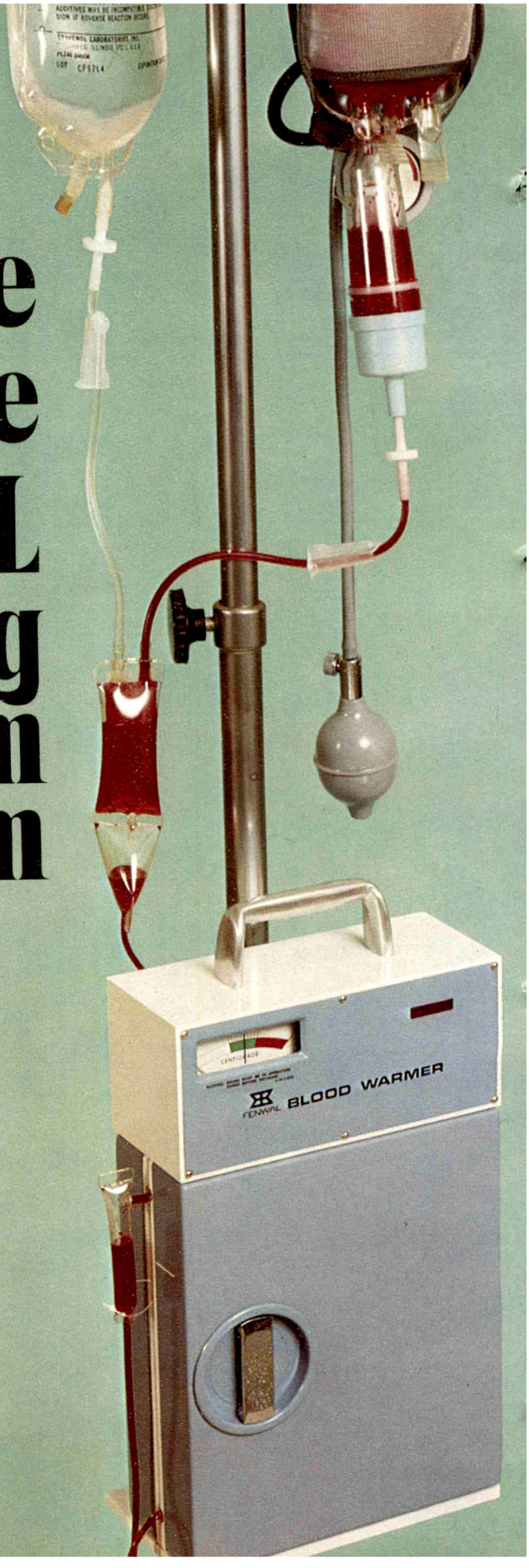
U.S. Patent No. 3,141,823

9/74

McNEIL
McNeil Laboratories, Inc.
Fort Washington, Pa. 19034


Our best
to your
surgical
patients
BLOOD WARMER

The complete FENWAL operating room system



The Fenwal Dry Heat Blood Warmer is designed for use during single or multiple transfusions when precise regulation of blood temperature and flow rate is indicated. It utilizes a disposable plastic blood-warming pathway.

Fenwal Recipient Sets are available to accommodate your infusion requirements. The Single Lead Set is to be used for the intravenous administration of one unit of whole blood, red cells or plasma. The "Y" Recipient Set is designed to permit dual hookups for simultaneous administration of blood and/or solutions. The Triple Lead Set may be employed in multiple infusion procedures, i.e., blood, solutions, blood components and medication.

The Fenwal Microaggregate Blood Filter is designed to remove microaggregates down to 20 microns in size during intravenous administration of stored whole blood or red cells.

Fenwal Pressure Infusors provide an efficient non-air-dependent method for the rapid infusion of whole blood or red cells.

The Fenwal TYPENEX™ Blood Recipient Identification System ties together the identity of the transfusion candidate, his cross-match request form, blood sample and up to 10 cross-matched units of blood.

The Fenwal Venous Pressure Manometer Set is a disposable, preassembled unit that permits continuous monitoring of the patient's venous pressure while performing one simple hookup.

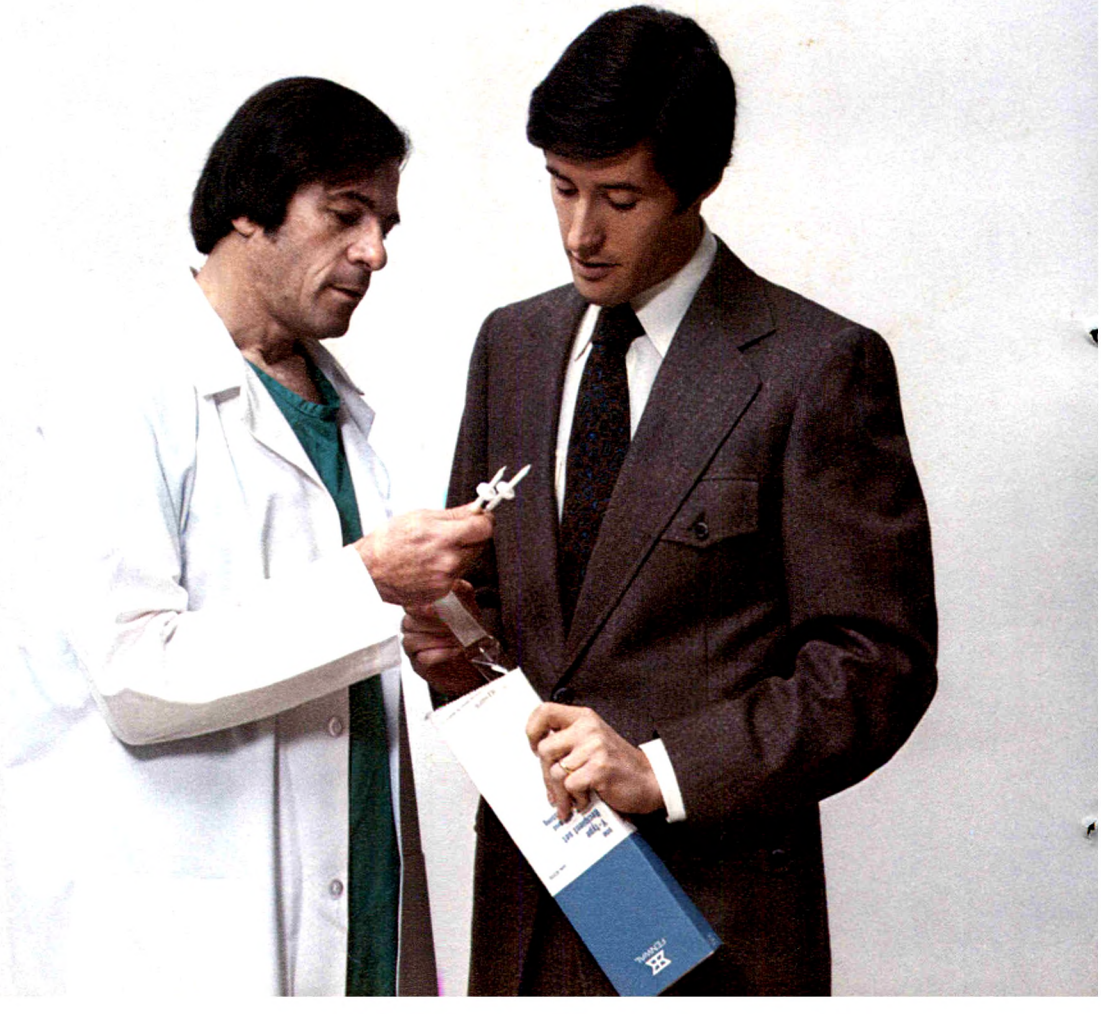
The Fenwal Platelet Recipient Set is designed specifically for the infusion of fresh blood and pool platelet concentrates.

Our best to you

Fenwal Laboratories has long been identified with innovation in modern blood handling systems. Our knowledge and experience in developing and providing sophisticated blood processing systems have earned a reputation for excellence. Thoroughly researched and tested to meet the demands of the medical profession, you can expect the same quality in Fenwal operating room devices that helped achieve our recognition with the nation's blood banks.

The Fenwal Specialist in your hospital can provide you and the other members of the operating team with completely detailed information on all of our products. Intensive training makes him fully qualified to answer your most involved questions regarding up-to-date blood transfusion procedure. Be sure to see your Fenwal Specialist the next time he visits your department.

FENWAL LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois, U.S.A. 60015.



When you need to know

DINAMAP for **non-invasive,** routine monitoring of arterial pressure.‡

Using: An ordinary pressure cuff with no transducer. Easily attached to any limb.*

Provides: Automatic determination and digital display of mean arterial pressure.

Write or call for your demonstration.

Applied Medical Research
6 Columbia Drive
Tampa, Fla. 33606
(813) 251-8390 Dept. 3

‡Audible pulse monitor optional
*Including patient preferred ank

Selected cases for Ketalar® (ketamine HCl injection)

(and a caution)

There are certain situations where the advantages of Ketalar suggest its serious consideration.

Four such hypothetical situations are detailed here. A fifth hypothetical case illustrates a situation in which Ketalar probably should be used only with caution.

Geriatric surgical procedure

Ketalar offers advantages in minor rectal surgery on elderly patients. When properly administered, Ketalar usually does not depress the patient's blood pressure or pulse rate, which can be a distinct advantage with any patient who is likely to develop hypotension. Further, emergence reactions normally are not a problem with patients in the older age group (over 65).

Severely burned patients

Patients with severe burns—and particularly children—are often excellent cases for Ketalar. In children, Ketalar offers rapid surgical anesthesia (generally within three to four minutes) at a range of 9 to 13 mg/kg, with the effect lasting from 12 to 25 minutes (the time intervals are for IM, not IV). Intramuscular administration avoids the possible difficulty in locating the vein in burn patients (particularly helpful in children where the veins are small). IM administration is also convenient and effective for repeated short-term anesthesia for such procedures as changing burn dressings, and skin grafts.

Manipulative diagnostic procedure

Ketalar facilitates diagnostic procedures in which the patient must be moved freely, and in which the maintenance of unaided respiration is essential. The pneumoencephalogram is an example. Once anesthesia is established, the patient can be transferred from a supine to an upright, supported position with ease since Ketalar maintains adequate unaided respiration, and there is minimal relaxation of the skeletal muscles.

Emergency room treatment

A good case for Ketalar can be made for use in accident victims with unknown medical histories brought to the emergency room. In the absence of positive medical history, Ketalar can be a useful agent because of its wide margin of safety. Consideration should be given to the effects of a significant increase in blood pressure, hypersensitivity to the drug, and an elevation in cerebrospinal fluid pressure. Ketalar also provides the benefit of rapid onset, and decreases the chance of aspiration because of active laryngeal-pharyngeal reflexes.

A caution:

Caution should be exercised when administering Ketalar to patients who are known to be alcoholics or who are acutely alcohol-intoxicated as such patients may be prone to untoward reactions.

Please see following page for brief summary of prescribing information.

advancement in anesthesiology
Ketalar
(Ketamine HCl injection)
Parke-Davis

advancement in anesthesiology

Ketalar
(Ketamine HCl injection)

Brief summary of prescribing information.

SPECIAL NOTE

EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12% OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT, DREAMLIKE STATES, VIVID IMAGERY, HALLUCINATIONS, AND EMERGENCE DELIRIUM. IN SOME CASES, THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY LASTS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETALAR.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE YOUNG (15 YEARS OF AGE OR LESS) AND ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY.

THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS. IN ADDITION, THE USE OF A SMALL HYPNOTIC DOSE OF A SHORT-ACTING OR ULTRASHORT-ACTING BARBITURATE MAY BE REQUIRED TO TERMINATE A SEVERE EMERGENCE REACTION. THE INCIDENCE OF EMERGENCE REACTIONS IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

WHEN KETALAR IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

INDICATIONS

Ketalar (ketamine HCl injection) is recommended:

1. as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketalar is best suited for short procedures but it can be used, with additional doses, for longer procedures;

2. for the induction of anesthesia prior to the administration of other general anesthetic agents;

3. to supplement low-potency agents, such as nitrous oxide.

CONTRAINDICATIONS

Ketamine hydrochloride is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard and those who have shown hypersensitivity to the drug.

WARNINGS

1. Ketalar should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration.

2. Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.

3. Barbiturates and Ketalar, being chemically incompatible because of precipitate formation, *should not* be injected from the same syringe.

4. Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar.

5. Postoperative confusional states may occur during the recovery period.

6. Respiratory depression may occur with overdosage or too rapid a rate of administration of Ketalar, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

Usage in Pregnancy

Since the safe use in pregnancy, including obstetrics (either vaginal or abdominal delivery), has not been established, such use is not recommended.

PRECAUTIONS

1. Because pharyngeal and laryngeal reflexes are usually active, Ketalar (ketamine HCl injection) should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if Ketalar is used alone. Muscle relaxants, with proper attention to respiration, may be required in both of these instances.

2. Resuscitative equipment should be ready for use.

3. ***The incidence of emergence reactions may be reduced*** if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note).

4. The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced pressor response.

5. In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain.

6. Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.

7. An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure.

ADVERSE REACTIONS

Cardiovascular: Blood pressure and pulse rate are frequently elevated following administration of Ketalar. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.

Respiration: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of Ketalar (ketamine HCl injection). Laryngospasms and other forms of airway obstruction have occurred during Ketalar anesthesia.

Eye: Diplopia and nystagmus have been noted following Ketalar administration. It also may cause a slight elevation in intraocular pressure measurement.

Psychological: (See Special Note).

Neurological: In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures (see Dosage and Administration).

Gastrointestinal: Anorexia, nausea and vomiting have been observed; however this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness (see Dosage and Administration).

General: Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

DOSAGE AND ADMINISTRATION

Preoperative Preparations:

1. While vomiting has been reported following Ketalar administration, airway protection is usually afforded because of active laryngeal-pharyngeal reflexes. However, since these reflexes may also be diminished by supplementary anesthetics or muscle relaxants, the possibility of aspiration must be considered. Ketalar is recommended for use in the patient whose stomach is not empty when, in the judgment of the practitioner, the benefits of the drug outweigh the possible risks.

2. Atropine, scopolamine, or other drying agent should be given at an appropriate interval prior to induction.

Dosage

As with other general anesthetic agents, the individual response to Ketalar (ketamine HCl injection) is somewhat varied depending on the dose, route of administration, and age of patient, so that dosage recommendation cannot be absolutely fixed. The drug should be titrated against the patient's requirements.

Onset and Duration:

Because of rapid induction following the initial intravenous injection, the patient should be in a supported position during administration.

The onset of action of Ketalar (ketamine HCl injection) is rapid; an intravenous dose of 2 mg/kg (1 mg/lb) of body weight usually produces surgical anesthesia within 30 seconds after injection, with the anesthetic effect usually lasting five to ten minutes. If a longer effect is desired, additional increments can be administered intravenously or intramuscularly to maintain anesthesia without producing significant cumulative effects.

Intramuscular doses, from experience primarily in children, in a range of 9 to 13 mg/kg (4 to 6 mg/lb) usually produce surgical anesthesia within three to four minutes following injection, with the anesthetic effect usually lasting 12 to 25 minutes.

Induction:

Intravenous Route: The initial dose of Ketalar administered intravenously may range from 1 mg/kg to 4.5 mg/kg (0.5 to 2 mg/lb). The average amount required to produce five to ten minutes of surgical anesthesia has been 2 mg/kg (1 mg/lb).

NOTE: The 100 mg/ml concentration (S-V 1585) of Ketalar, *should not* be injected intravenously without proper dilution. It is recommended the drug be diluted with an equal volume of either Sterile Water for Injection, USP, Normal Saline, or 5% Dextrose in Water.

Rate of Administration: It is recommended that Ketalar be administered slowly (over a period of 60 seconds). More rapid administration may result in respiratory depression and enhanced pressor response.

Intramuscular Route: The initial dose of Ketalar administered intramuscularly may range from 6.5 to 13 mg/kg (3 to 6 mg/lb). A dose of 10 mg/kg (5 mg/lb) will usually produce 12 to 25 minutes of surgical anesthesia.

Maintenance of Anesthesia:

Increments of one half to the full induction dose may be repeated as needed for maintenance of anesthesia. However, it should be noted that purposeless and tonic-clonic movements of extremities may occur during the course of anesthesia. These movements do not imply a light plane and are not indicative of the need for additional doses of the anesthetic.

It should be recognized that the larger the total dose of Ketalar (ketamine HCl injection) administered, the longer will be the time to complete recovery.

Supplementary Agents:

Ketalar is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained.

HOW SUPPLIED

Ketalar is supplied as the hydrochloride in concentrations equivalent to ketamine base.

N 0071-4581-15—Each 50-ml vial contains 10 mg/ml. Supplied in cartons of 10.

N 0071-4581-12—Each 20-ml vial contains 10 mg/ml. Supplied in cartons of 10.

N 0071-4582-10—Each 10-ml vial contains 50 mg/ml. Supplied in cartons of 10.

N 0071-4585-08—Each 5-ml vial contains 100 mg/ml. Supplied in cartons of 10.

PD-JA-1839-1-P (4-76) SG

PARKE-DAVIS

PARKE, DAVIS & COMPANY
Detroit, Michigan 48232

PI Peripheral Nerve Stimulator

Monitors Muscle Relaxants

The PI Peripheral Nerve Stimulator monitors effects of skeletal muscle relaxants on the neuromuscular junction, detects abnormal response to muscle relaxants and distinguishes between depolarizing and non-depolarizing blockade.

Model NS-2

The NS-2 is now in use in many hospitals throughout the U. S. and abroad. It is designed primarily for use during surgery and delivers stimuli automatically at 5-second intervals. One or fifty pulses-per-second may be selected by momentary push-button switches. Output is a monophasic square wave pulse. Amplitude of the pulse is linearly adjustable. A flashing red light indicates low battery voltage. The NS-2 is solid state, rugged, battery powered, portable and lightweight.

Model NS-3

The NS-3 represents the latest in solid state technology. Use of integrated circuits has made it possible to build a very compact and versatile stimulator. Its miniature size makes the NS-3 more convenient for preoperative and postoperative testing. It delivers stimili at one second intervals when the rocker switch is depressed to the TWITCH position. A fifty-pulses-per-second rate may be selected by depressing the rocker switch to the momentary TETANUS position. Output is a monophasic square wave pulse. Amplitude of the pulse is linearly adjustable. The NS-3 also has a low-battery-voltage indicator.

Professional Instruments Company

General Office and Sales
Brookhollow Plaza, Suite C-5, 4800 W. 34th Street
P.O. Box 38245, Houston, Texas 77092

Professional Medical and Scientific Instrumentation

ANTILIRIUM
(Physostigmine Salicylate)

REVERSES MOST POST-OPERATIVE DELIRIUM AND PROLONGED SOMNOLENCE

Before prescribing, please consult complete product information, a summary of which follows:

ACTION: ANTILIRIUM (physostigmine salicylate) is a salicylic acid derivative of an alkaloid extracted from seeds of Physostigma Venenosum (calabar bean). The action of the parasympathetic nerves is intermediated by the formation of acetylcholine at the peripheral end of these nerves. Physostigmine inhibits the destructive action of cholinesterase and thereby prolongs and exaggerates the effect of the acetylcholine.

Physostigmine contains a tertiary amine and easily crosses the blood brain barrier, while neostigmine contains a quaternary amine and is not capable of crossing the structure. This may explain why neostigmine does not cause reversal of anticholinergic-induced delirium while physostigmine does.

INDICATIONS: TO REVERSE THE TOXIC EFFECTS UPON THE CENTRAL NERVOUS SYSTEM CAUSED BY DRUGS IN CLINICAL OR TOXIC DOSAGES CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING.

SEVERE ANTICHOLINERGIC POISONING MAY PRODUCE: COMA, MEDULLARY PARALYSIS AND DEATH.

CENTRAL TOXIC EFFECTS MAY INCLUDE: HALLUCINATIONS, DELIRIUM, DISORIENTATION, ANXIETY AND HYPERACTIVITY.

Dramatic reversal within minutes of coma, hallucinations, and other signs can be expected if the diagnosis is correct and the patient has not suffered anoxia or other insult. Therapeutic doses may be necessary at intervals as life-threatening signs recur. Physostigmine is destroyed in the body in 60 to 120 minutes.

CONTRAINDICATIONS: Physostigmine should not be used in the presence of asthma, gangrene, diabetes, cardiovascular disease, mechanical obstruction of the intestines or urogenital tract or any vagotonic state, and in patients receiving choline esters or depolarizing neuromuscular blocking agents.

WARNING: If excessive symptoms of salivation, emesis, urination and defecation occur, the use of ANTILIRIUM should be terminated. If excessive sweating or nausea occur, the dosage should be reduced.

Intravenous administration should be at a slow, controlled rate, no more than 1 mg. per minute (see dosage). Rapid administration can cause bradycardia, hypersalivation leading to respiratory difficulties and possibly convulsions.

An overdosage of ANTILIRIUM can cause a cholinergic crisis.

PRECAUTIONS: Because of the possibility of hypersensitivity in an occasional patient, atropine sulfate injection should always be at hand since it is an antagonist and antidote for physostigmine.

ADMINISTRATION AND DOSAGE: The usual adult dose of ANTILIRIUM is 0.5 to 2.0 mg. intramuscularly or intravenously. Intravenous administration should be at a slow, controlled rate of no more than 1 mg. per minute. It may be necessary to repeat dosages of 1 mg. to 4 mg. at intervals as life threatening signs such as arrhythmias, convulsions and deep coma recur.

IN ALL CASES OF POISONING, THE USUAL SUPPORTIVE MEASURES SHOULD BE UNDERTAKEN.

SUPPLIED: 2 ml. ampules containing:
PHYSOSTIGMINE SALICYLATE 1 mg. per ml.
Packed 12 ampules per box.
NDC 0456-1037-12

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES:

Greene, L. T.: Physostigmine treatment of anticholinergic drug depression in postoperative patients. Anesth & Analg, March-April 1971; 50-2: 222-226.

Rumack, B.: Anticholinergic poisoning: Treatment with physostigmine. Pediatrics, Sept. 1973.

Slovis, T. L., Ott, J. E., Tietelbaum, D. T., and Lipscomb, W.: Physostigmine therapy in acute tricyclic antidepressant poisoning. Clinical Toxicology, 4:451, 1971.

DRUGS AND CHEMICALS CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING:

- AMITRIPTYLINE (Elavil, Triavil, Etrafon)
- ANISOTROPINE METHYLBROMIDE
- ATROPINE
- BELLADONNA
- BENACTYZINE
- CHLORPHENIRAMINE
- CYCLOPENTOLATE
- DESIPRAMINE (Norpramin, Pertofrane)
- DICYCLOMINE
- DIPHENHYDRAMINE
- DOXEPIN (Sinequan)
- HOMATROPINE
- HYOSCINE
- HYOSCYAMUS
- IMIPRAMINE (Tofranil, Presamine)
- ISOPROPAMIDE
- MEPENZOLATE
- METHANTHELINE
- METHAPYRILENE
- NORTRIPTYLINE (Aventyl)
- PIPENZOLATE BROMIDE (Piptal)
- PROPANTHELINE
- PROTRIPTYLINE (Vivactil)
- PYRILAMINE
- SCOPOLAMINE
- STRAMONIUM
- PHENOTHIAZINES
- TRICYCLIC ANTIDEPRESSANTS (Aventyl, Elavil, Etrafon, Norpramin, Pertofrane, Presamine, Tofranil, Triavil, Vivactil)
- THIORIDAZINE (Mellaril)

O'NEAL, JONES & FELDMAN, INC.

2510 METRO BLVD. • ST. LOUIS, MO. 63043 • (314) 569-3610

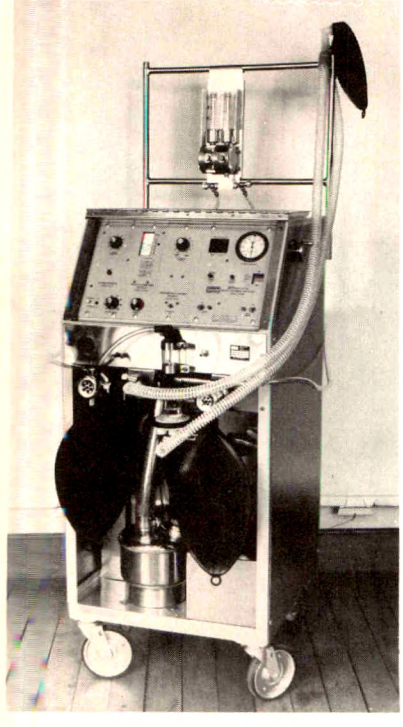
EMERSON IMV Ventilator

Intermittent Mandatory Ventilation

Continuous-flow voluntary ventilation, with intermittent forced breaths, is an alternative to assisted or controlled respiration. It has been found especially valuable for infants and for use in "weaning" adults as they improve.

Air fully humidified (and usually enriched with oxygen) flows continuously to a reservoir bag, and is available for unobstructed inspiration by the patient. A slight expiratory back-pressure (PEEP) may be added, to keep the lungs expanded. At intervals the ventilator delivers a "mandatory" breath, which supplements the patient's own breathing activity and increases minute volume. The machine does not have to "take over". The patient maintains his own homeostasis, without interference from drugs or hyperventilation.[1]

At first the ventilator is generally set to supply mandatory breaths at a normal controlled rate. This controlled respiration is then gradually changed, by lengthening the interval between breaths (a second or two at a time) as the patient's condition improves. Eventually mandatory breaths are spaced so far apart that the patient scarcely relies on them at all — and "weaning" is completed.[2]



VERSUS ASSIST

Triggering an assistor has often been a problem, particularly for infants, since their rates are rapid and their inspiratory impulses are slight. If synchronization is less than perfect, the patient inhales (at least part of the time) with no fresh gas available. Under such circumstances, blood levels of CO_2 rise, as noted by Kirby and associates.[1]

VERSUS CONTROL

For apneic patients, control is obviously needed. But to take over, when a patient is breathing spontaneously, drugs have to be used or the patient has to be hyperventilated. Either procedure has drawbacks. Paralytic or sedative agents may obscure signs of neurological or metabloic disorders. Lowered muscle tone may impair venous return, and hence cardiac output. The effects of such drugs are particularly hard to predict in infants.

Hyperventilation (often used to suppress spontaneous breathing efforts) has drawbacks, too. The resultant alkalosis reduces cerebral blood flow. Blood levels of calcium and magnesium are altered. Airway resistance increases and pulmonary compliance decreases with hypocarbia.[3] Finally, there is evidence of a shift in the carbon dioxide response curve, which makes weaning more difficult.

All of these pit-falls can be avoided by using continuous-flow IMV.

Please request Form 3-MV.

J. H. EMERSON COMPANY

CAMBRIDGE, MASSACHUSETTS 02140

51ST CONGRESS

MARCH 6-10, 1977

International Anesthesia Research Society

DIPLOMAT RESORT AND COUNTRY CLUBS
HOLLYWOOD, FLORIDA

IMPORTANT INFORMATION ON THE 51st CONGRESS

Pre-registration Material, Program, Hotel Card—will be mailed in mid-December to all I.A.R.S. members, associate members, and educational members. (Members outside of U.S., Canada and Mexico who plan to attend, please advise I.A.R.S. Cleveland office by December 1 to assure timely arrival of pre-registration material.)

Scientific Exhibits—Application forms are available from B. B. Sankey, M.D., Executive Secretary, I.A.R.S., 3645 Warrensville Center Rd., Cleveland, Ohio 44122. There is no deadline for applications; however, applications received after November 1, 1976, are subject to exhibit space availability.

Technical (Commercial) Exhibits—Applications available from Charles B. Slack, Inc., Exhibit Manager, 6900 Grove Rd., Thorofare, New Jersey 08086.

C.M.E. Credit—This Continuing Medical Education offering meets the criteria for Category 1 credit (22 hours est.) for the Physician's Recognition Award of the American Medical Association.

Anesthesia for the Patient with Cardiac Disease: Preamble

EMERSON A. MOFFITT, MD*

THE number of people with coronary arterial disease including those who have had a myocardial infarction, increases as the total population increases and as more people live to an older age. Hence, the number of patients with cardiac disease requiring some form of anesthesia for operation or diagnostic procedure should continue to grow steadily.

In 1974, there were 16,486,045 surgical procedures in the United States,[1] in a total population of approximately 215,000,000. That is, 1 person in 7 had an operation. Tarhan's group[2] showed that in a large-volume anesthetic practice, 13 patients per 1000, over 30 years of age, came for operation with evidence of a previous myocardial infarction. There are no reasons to believe that this incidence is different for the surgical population of North America in general. Hence, in the United States in 1974, about 214,500 patients with a previous infarction had a surgical procedure. Tarhan's work also identified the high incidence of recurrent infarction (6.6%) in this patient group, and the inordinately high mortality rate (54%) compared to infarction without operation.

In addition to the candidates for anesthesia who have had a previous infarction, a much larger group of patients have serious heart disease without having had a frank coronary occlusion. With approximately 5 percent of the population over 18 years having known or suspected coronary disease[2] and 1/7 undergoing an operation, several million patients with cardiac disease are anesthetized each year in the United States.

Everyone practicing anesthesia faces the patient with cardiac disease every week—perhaps almost every day. It behooves us to be perceptive of their increased risk of anesthesia and operation, so that we may best assure a safe course. For these reasons, the panel will examine the sound principles and good practices essential to successful management of the cardiac patient having an operation for other than cardiac surgery.

REFERENCES

1. ASA Newsletter. 39:9, 1975

2. Tarhan S, Moffitt EA, Taylor WF, et al: Myocardial infarction after general anesthesia. JAMA 220:1451-1454, 1972

*Professor and Head, Department of Anaesthesia, Faculty of Medicine, Dalhousie University, Halifax, Canada.

This panel was presented at the 50th Congress of the International Anesthesia Research Society, March 14-18, 1976, Phoenix, Arizona.

The Patient with Heart Disease: Preoperative Evaluation and Preparation

ALAN H. GOLDBERG, MD, PhD*

THE surgical patient with heart disease and diminished cardiac compensation has decreased cardiac output and decreased tissue perfusion.

We are concerned about this patient for several reasons. Because of his increased intravascular volume, the management of his fluid and electrolyte replacement becomes very complicated. He is a candidate for thromboembolic phenomena such as pulmonary emboli. With decreased ventilation, there is increased likelihood for hypoxia and hypercarbia as well as respiratory infections and pneumonia. He has impaired liver and kidney function, which can change the effects of drugs. In addition, the various stresses to which a surgical patient is exposed can push him into acute heart failure. Failure may be precipitated by pain, fear, or apprehension, or with the induction of general anesthesia. He may be inadvertently given too much fluid for his cardiac status.

This patient may also get into trouble in the postoperative period. Inability to achieve a needed rise in cardiac output may result in acute pulmonary edema or the low output-cardiac failure syndrome, with low urine volume, vasoconstriction, and hypotension. There appears to be a significantly greater postoperative mortality in patients who are not able to increase their cardiac output in response to the metabolic demands of operation and postoperative stress.

However, it is not the patient with overt failure whose cardiac status will be missed and who will come to surgery without some form of therapy; it is easy to recognize the patient with severe dyspnea, edema, enlarged heart, or a loud murmur. It is the patient with borderline incipient failure who was not recognized immediately as being in failure who may go on to have stress-precipitated severe failure.

The typical patient who gets into trouble is one of the following:

(1) The patient with rheumatic heart disease with mitral stenosis.

(2) The patient with aortic stenosis, particularly an elderly patient who may not have a very impressive murmur. This patient is in a precarious state and tolerates operation, anesthesia, and acute trauma poorly.

(3) The patient with chronic lung disease. He may have some hypoxia, and some pulmonary hypertension. This patient may be in borderline right-sided compensation and may not be recognized as having serious underlying pulmonary and cardiac disease.

With these patients, it is important to keep in mind the concept of cardiac reserve. As cardiac capacity fails, compensatory adjustments take place. Increased adrenergic activity develops, the heart increases in size, and the heart rate increases. The individual may continue to carry out his regular activities and may be free of severe symptoms of failure, yet he may have pretty well used up his cardiac reserve, so that if any more stress is superimposed, he will go into failure.

Assessment of Cardiac Function.—In the past decade, many new technics have been developed for assessment of myocardial function. These are mainly sophisticated laboratory technics, for the catheterization

*Clinical Director, Department of Anesthesiology, Boston City Hospital; Professor and Associate Chairman, Department of Anesthesiology, Boston University School of Medicine, Boston, Massachusetts 02118.

laboratory. In the clinical situation, however, we must still employ simple bedside tools, primarily the history and the physical examination.

Concerning the history, a major warning symptom in the patient with incipient failure is cough, particularly nocturnal cough. If you elicit the history of a patient who has started to cough at night but is not raising much in the way of sputum, and each time he assumes the recumbent position he starts to cough, that suggests he is developing a shift of edema fluid into the pulmonary vasculature and that his cough reflex is being stimulated. This patient may have normal physical findings on chest auscultation and even on chest x-ray.

Insomnia is another insidious symptom of impending left heart failure. This may be related to restlessness due to respiratory distress which is not recognized as dyspnea or cough. In the absence of any history of prostatism or bladder infection, the person who has to get up 2 or 3 times at night to void may be describing early evidence of congestive heart failure. The mechanism for regulating salt and water balance is disturbed in patients with incipient heart failure and no longer follows the normal pattern of urine volume formation. This patient will form more urine at night and will therefore have to get up to void.

Unexplained fatigue is another manifestation of incipient heart failure. Irritability or restlessness can be due to decreased cerebral blood flow due to inadequate cardiac output.

Abdominal discomfort, indigestion, or pain, particularly right upper quadrant pain, suggests distention of the liver capsule.

One of the compensatory mechanisms in failure is increased sympathetic activity. This results in increased perspiration. In the absence of fever or other reasons for sweating, a patient who perspires heavily may be in early failure.

The patient may describe dyspnea on effort, but you have to distinguish this from hyperventilation. The patient with dyspnea is breathing rapidly and shallowly, whereas the person with hyperventilation sighs and takes deep breaths. He tells you he cannot get enough air and he may say that breath goes only half way down. This type of complaint is not characteristic of dyspnea on exertion.

Also the rapidity of onset of dyspnea is a valuable clue. Dyspnea due to chronic lung disease generally has a slow onset and is progressive over a long period of time. Recent onset of dyspnea suggests cardiac disease.

Looking further into the history, has the patient been receiving any medication that might impair cardiac function? For example, propranolol, a beta-adrenergic blocking agent, is used as therapy in a number of disorders, as well as for prophylaxis against arrhythmias. Taken over an extended period of time, particularly in large doses, this drug can impair ventricular function. If the drug can be discontinued, especially in the patient who is in a low output state with decreased left ventricular reserve and compensated failure, this should be done 2 or 3 days before operation. If it cannot be discontinued (as in the patient with angina), the antagonist is isoproterenol, which is a beta-adrenergic stimulant.

Physical Examination.—One of the subtle findings of heart failure is persistent unexplained sinus tachycardia. A rate of 90 to 100 bpm may be a manifestation of increased sympathetic activity, which is compensating for impaired cardiac reserve. If this cannot be related to something like fear, apprehension, or fever, think of borderline failure.

Some patients with incipient left heart failure have a potent element of bronchoconstriction that may present as asthma or wheezing, when in fact it reflects pulmonary vascular distention due to the cardiac condition.

Pulsus alternans, observed when feeling the arterial pulse, also detects impaired left ventricular function. The rhythm of the beat in pulsus alternans is perfectly regular, without any interruption. It is not a bigeminal rhythm, but manifests in alternating variations in the peak systolic pressure and the rate of rise of pressure. This can be detected with the blood pressure cuff when a larger systolic peak alternates with a smaller one. In palpation also, you get the impression of a slightly alternating forcefulness of the arterial pulse. It is more easily detected in the carotid or the brachial than in the radial pulse.

If the patient has a slight murmur across the outflow tract of the left ventricle, as in an elderly patient, for example, with some atherosclerotic change in the aorta or the

aortic valve, pulsus alternans translates itself into murmur alternans. If you listen carefully, the faint systolic murmur, which is of no hemodynamic consequence, may give you the clue that the left ventricle is alternating its forcefulness of ejection. The rhythm is regular but the forcefulness or intensity of the murmur varies, showing that the left ventricular myocardium is functioning poorly. This subtle sign of failure may be present even though the patient may not be in overt failure with pulmonary edema or congestion.

The neck veins should be examined. The external jugular vein, which is often tortuous and partly compressed, may be distended even in the *absence* of true elevaof venous pressure. Also, the presence of competent valves at the lower ends of these veins prevents a satisfactory retrograde transmission of the venous pulse wave. At the bedside, elevation of venous pressure can best be observed in the area between the 2 insertions of the sternocleidomastoid muscle, which lies over the internal jugular vein. The pulsations of the internal jugular vein cause fairly diffuse pulsations of the skin overlying this area, reflecting the underlying venous pulsations. If you can see these pulsations extending upward into the middle of the neck or up to the angle of the jaw, in a patient sitting upright, this is an important clue that central venous pressure is significantly elevated.

Auscultation of the Heart.—Gallops are diastolic events related to 2 periods of filling of the ventricles. S_3, related to the rapid filling phase, is the ventricular diastolic gallop. S_4, related to the presystolic filling phase and atrial systole, is the atrial gallop. These are low-frequency sounds and are best heard over the ventricle at the apex, listening with a very light pressure with the bell piece of your stethoscope. A gallop rhythm is one of the earliest clinical clues to heart disease and affords valuable bedside information concerning diagnosis, prognosis, and treatment.

The ventricular diastolic gallop (S_3) is frequently one of the first detectable signs of serious heart disease and/or cardiac decompensation. If you listen carefully in the patient turned in the left lateral position, and hear this type of triple rhythm, significant left ventricular disease is possibly present, especially if the patient is over age 40.

The ECG should of course be examined. However, this does not really tell you much about failure. If it shows left ventricular hypertrophy or intraventricular conduction disturbance, these suggest left ventricular impairment, but the ECG cannot tell you whether the patient is well compensated or not. It can, however, alert you to the possibility of infarction, ischemic disease, or rhythm disturbance.

The Value of Chest X-ray.—Characteristic of a patient in congestive heart failure is the so-called butterfly pattern, in which the heart is considered to be the body of the butterfly and the pulmonary edema is the wings. This pattern, due to intra-alveolar edema, results in radiodensities that are most prominent in the inner and middle zones of the lung. This is not a subtle sign of failure, as the patient will be in pulmonary edema.

A sign seen very early in the course of failure is the Kerley-B line, a linear density caused by thickening of the intralobular septa due to an increase in pulmonary venous pressure. These densities are represented by fine horizontal lines in the costophrenic angles.

What To Do About Heart Failure.—If you have the time, it is better to undertake digitalization and diuretic therapy deliberately over a period of 2 to 3 days, rather than to have to move in with acute digitalization. But if the patient requires early and immediate operation, you can digitalize rapidly, using IV digoxin. Given IV, this drug has a rapid onset of action, reaching its peak effect in about 2 to 3 hours and has a strong effect even before that. Since you can continue to use the same drug thereafter, it probably represents the agent of choice even in the circumstances of fairly rapid digitalization.

Diuretics should also be given. However, these may cause a loss of potassium, which represents a hazard through digitalis intoxication, with consequent arrhythmias. For this reason, it is advisable to monitor the serum K^+ levels carefully and replace K^+ as needed.

Another problem associated with the use of diuretics is excessive reduction of effective circulating blood volume. The physician's zeal to obtain a dry weight, to eliminate peripheral edema, and to lower distended neck veins may carry the patient too far back on the ascending limb of the Starling curve and may deprive the patient

of needed ventricular filling pressure. Because these patients may need a somewhat increased filling pressure, it is best to hedge on the side of under- rather than overdiuresis.

The same principle applies to digitalis. It is wise to underdigitalize rather than overdigitalize, to avoid such problems associated with digitoxicity as ventricular premature contractions or heart block.

Many subtle signs and symptoms of diminished cardiac compensation may be present before the onset of decompensation. These should be looked for and the appropriate therapy instituted before overt heart failure occurs.

AORTOCORONARY VEIN GRAFT FLOW. Flow through aortocoronary saphenous vein grafts and augmentation by direct intragraft injection of coronary vasodilators has prognostic importance with respect to subsequent graft closure. Following injection of sodium nitroprusside, 50 μg, directly into the graft, flow increased from 40.1 ± 4.5 to 81.3 ± 8.5 ml/min. This effect dissipated in 1.5 to 4 minutes and was not associated with statistically significant changes in blood pressure or heart rate and cardiac dysrhythmias did not occur. Similar flow changes occurred with 30 mg papaverine but the response required longer to be manifest and was associated with a greater decrease in blood pressure and a higher incidence of dysrhythmias. Furthermore, the pH of sodium nitroprusside is 7.6 and thus less likely to irritate vein intima than the more acidotic papaverine (pH 3.4). Nitroprusside may be the drug of choice for intragraft injection when immediate flow augmentation is necessary. *(Larsen PB, Yeh BK, Gentsch TO et al: Sodium nitroprusside as a coronary vasodilator in man: A comparison to the effects of sodium nitroprusside and papaverine hydrochloride on aortocoronary saphenous vein graft flow. Ann Thor Surg 21:16-18, 1976)*

Anesthetic Management

WENDELL C. STEVENS, MD*

"INADEQUATE cardiac performance can result from a severe stress imposed upon a subsystem with normal reserves, a mild stress upon one with minimal reserves, or something in between."[1] The majority of patients with heart disease tolerate anesthesia, operation, and the postoperative period without apparent irreversible worsening of cardiac function. This is true even when the heart itself is the site of operation. Although stress occurs, cardiac reserves are usually adequate to allow the patient to tolerate the stress.

Sechzer's group,[2] studying whether any of a number of events served to predict myocardial stress in patients with arteriosclerotic vascular disease, undergoing major vascular operations, found no relationship between myocardial injury and the degree of intraoperative circulatory lability, duration of hypotension, duration of operation, or volume of blood replacement. Perhaps the failure to correlate these events means stress cannot be thought of in terms of only one variable.

For example, lowering arterial pressure (AP) may decrease coronary blood flow if coronary vasodilation cannot occur. However, if myocardial O_2 demand decreases appropriate to the decrease in coronary perfusion, myocardial injury may not occur. On the other hand, increasing AP may increase coronary blood flow, but if myocardial O_2 demand increases disproportionately, myocardial ischemia may develop. The greatest threat of ischemia exists in those portions of the myocardium subject to the greatest intramural pressures relative to coronary perfusion pressure.[3]

My goal will be to describe some of the circulatory changes we expect from anesthesia, to comment briefly on the stress of operative and recovery periods, and to describe the options available when a patient with cardiac disease requires anesthesia. Some of the changes these drugs induce might be thought of as stresses; some, in fact, may be salutary. Much of the data must be extrapolated from patients with circulatory diseases investigated while about to undergo or while undergoing heart operations.

Anesthetic Agents.—The nonflammable, potent inhaled agents, halothane and enflurane, reduce cardiac output and AP.[4-6] Halothane increases right atrial pressure, apparently because the myocardial depression exceeds the ability of halothane to produce vasodilation. Enflurane also decreases cardiac output to the same degree as halothane, but decreases peripheral vascular resistance to a greater degree than halothane. Enflurane produces enough venodilation to prevent increases in right atrial pressure.

Stoelting's group,[7] measuring the intraoperative circulatory effects of halothane alone in patients undergoing heart-valve replacement, found that, at an alveolar halothane concentration of 0.55 percent, cardiac output was maintained, total peripheral resistance (TPR) decreased, and AP decreased slightly. Conahan's group[8] found that patients with valvular heart disease who received 50 percent N_2O and up to 1 percent inspired halothane showed significant decreases of AP, although the exact changes in cardiac output were not described. However, when compared with morphine, halothane tended to maintain cardiac output at a higher level, presumably because of the greater decrease of TPR with halothane.

Kemmotsu and associates[9] showed that the depression of myocardial function produced by heart failure was similar to that produced by halothane or enflurane when tested in isolated muscle strips. If failing muscle is exposed to halothane or enflurane, the drug-induced depression of contractility *begins* at a level of depressed heart function. Therefore, one can expect greater total depression from smaller doses of inhaled agents in failing than in normal hearts.

*Associate Professor, Department of Anesthesia, University of California, San Francisco, California 94143.

One may occasionally encounter profound hypotension with halothane, as with other agents, for reasons somewhat as follows: The heart uses a number of reserves in an effort to maintain cardiac output.[10] These include the Frank-Starling mechanism, development of myocardial hypertrophy, increased venous tone and arteriolar constriction, and increased sympathetic drive to the heart. The latter results in both contractility and heart-rate effects. Since parasympathetic control of the failing heart is defective[11] and decreased amounts of adrenergic transmitter are present in failing hearts,[12] these combined reserves function to maintain cardiac output and perfusion pressure. Anesthetic agents will alter one or more of these reserves. For example, if the reserve of increased blood volume has been reduced by diuretics and anesthesia produces a significant decrease in venous tone, one may see an inordinate decrease of cardiac output and blood pressure (BP).

While the addition of N_2O raises AP in healthy young volunteers,[13] N_2O may cause decrease of AP in patients with sick hearts under certain circumstances.[14] This may represent direct myocardial depression[15] or increased pulmonary or peripheral vascular resistances. The latter increases in afterload may result in reduced cardiac output.

These few data indicate that the stress imposed by potent inhaled agents will be primarily hypotension. However, because myocardial O_2 requirement will probably be reduced, the hypotension usually will be well tolerated.

Narcotic analgetics have been used for anesthesia in patients with heart disease, with an eye to maintenance of circulatory variables at awake levels.[14,16] The predominant circulatory effect of morphine is an early reduction of TPR, which returns to control values and may well rise above control values when operation begins. Lowenstein's group[17] demonstrated that cardiac output was maintained or increased and that only minor AP changes occurred, usually with decreases of TPR and increases of vascular capacitance in patients with valvular heart disease.

Comparison of Anesthetic Agents.—Somewhat greater decreases in AP will occur with halothane or enflurane; better preserved, or, with the onset of operation, increased AP may be expected with morphine. If pressure does increase during morphine anesthesia, one may be unable to reduce pressure consistently with additions of morphine.

In patients with valvular or coronary artery disease, ketamine can be expected to raise AP, primarily through increasing the heart rate.[18-20] According to Reves,[21] one is more likely to see decreases of AP with morphine than with ketamine in coronary artery disease patients, while in valvular heart disease patients, the circulatory effects, at least in terms of AP, are similar with morphine and ketamine.

Which is better: BP at or above awake values or decreased BP? Reves[21] measured the myocardial O_2 supply/demand ratio by application of the relation between diastolic pressure time index/tension time index.[3] The higher the ratio the better. Better indices occurred with the lower BP seen with morphine. The ECG showed reversal of injury patterns as well. It is likely that a BP at or slightly below awake values combined with a slow heart rate is favorable in such patients. Stanley[22] reported that when ketamine is administered concomitantly with halothane, greater circulatory depression will occur than if halothane alone is used.

Hence, one can choose an inhaled agent providing decrease of AP and cardiac output, morphine providing maintained or elevated BP and cardiac output, ketamine providing elevated BP primarily due to an increase of cardiac output from increased heart rate.

Barbiturates given by rapid IV injection influence circulatory variables significantly by producing venodilation.[23,24] Large doses of thiopental may produce myocardial depression.[25] Although a direct smooth-muscle constriction may be produced by thiopental,[26] the predominant circulatory effect of bolus administration will be vasodilation.

Diazepam[27] produces minor circulatory effects if given slowly and in small doses. It is used as a supplement to narcotic anesthesia, since narcotics produce sedation which is unpredictable in intensity or speed of onset.

The circulatory stress induced by spinal or epidural anesthesia is hypotension, which occurs because of sympathetic blockade with resultant venodilation and decreased cardiac output.[28] It is here, again, that the relation of myocardial O_2 demand to coronary perfusion is so important. Decreased myocardial O_2 demand due to slowing of heart rate,

decreased cardiac output, decreased filling pressure which may lead to decreased myocardial stretch or tension, and decreased ventricular afterload appears generally to allow tolerance of decreased coronary perfusion pressure. A patient with heart disease who has increased ventricular filling pressures, enlarged central blood volume, and relatively high systemic vascular resistance may be improved by sympathetic blockade. The circulatory effects of regional anesthesia are altered by epidural epinephrine administration, in that a greater loss of TPR and increased heart rates will occur.[29]

Sympathetic blockade can be avoided by peripheral nerve blocks—for instance, multiple intercostal blocks. In order to exploit this advantage of peripheral nerve block, however, several considerations apply. It may be important in a patient whose condition is precarious from ischemic heart disease to blunt the sympathetic stimulation of multiple injections by thorough explanation, use of a particularly gentle technic, and premedication.

Sapala and colleagues[30] recently described the incidence of cardiopulmonary complications in patients with arteriosclerotic vascular disease. Similar complication rates occurred after general or spinal anesthesia. Sapala measured a lower incidence of complications after local anesthesia but did not offer data on how anesthetics were chosen. Patients who exhibited arrhythmias or congestive heart failure without myocardial infarction had the lowest complication rates.

Effects of Operative Procedures.—Some events may enhance the stress of operation. Perhaps paramount is change of blood volume. The usual directional change is decreased blood volume resulting in reduced preload. Another stress which may not be apparent until the recovery period is change of body temperature. If temperature is increased intraoperatively, O_2 demand and hence need for increased cardiac output exist. More commonly, the temperature decreases in relation to exposure of viscera to ambient temperatures, increased duration of operation, use of muscle relaxants, cold IV solutions, and increased patient age.

Details of the effects of hypocapnea, hypercapnea, hypoxemia, changes in intrathoracic pressure and of adjuvant drugs, such as epinephrine, are beyond the scope of this discussion.

Postoperative Recovery.—Apparently, the greatest circulatory stresses occur in the postoperative period. For example, recurrent myocardial infarction occurs with greater frequency postoperatively than intraoperatively.[31] Events which place demands on the cardiac reserves include decreased body temperature, as mentioned above. Roe and coworkers[32] found that a temperature fall of between 0.3 to 1.2° C doubled postoperative O_2 consumption. Greater decreases in temperature occur in older patients; interestingly, elderly patients are less likely to increase O_2 consumption than young patients. Bay's group,[33] measuring requirements for cardiac output in postoperative patients who shiver, found 300 to 400 percent increases over normal values. The implications of this demand seem clear, although documentation of morbidity related to such increased cardiac work is not readily available.

Increased temperature will increase O_2 demand and hence cardiovascular stress. Tissue trauma also increases O_2 demand. It has long been known that demand for increased cardiac output follows operations.[34] Venous Po_2 falls postoperatively, suggesting that increased cardiac output may not compensate for increased O_2 demand. In any event, cardiac reserves are called into play.

Marshall and Wyche[35] nicely synthesized the usual postoperative hypoxemic events, showing that when hypoxemia occurs, cardiac reserves must be operative if O_2 delivery to the heart and other tissues is to be maintained. Of special significance is the relation of hypoxemia to site of operation. In subjects undergoing nonabdominal procedures, the maximum decrease in Pao_2 occurred immediately postoperatively and then rapidly returned toward normal. In abdominal operations, there was a much slower return to normal. The pulmonary complication rate also was greater following abdominal operations. With regional anesthesia, Pao_2 began to decrease several hours postoperatively and the sequence of changes thereafter was similar to that after general anesthesia used for similar operations.

Postoperative respiratory complications leading to deterioration of mechanical properties of lung will increase O_2 cost of breathing. Wilson and associates,[36] in studies done immediately after cardiac surgery, found this cost to be 29.7 $ml/m^2/min$, or 18 percent of the total O_2 requirement, compared with values of 1.4 to 4.2 $ml/m^2/min$ in subjects with normal lungs. The latter is equivalent to 1 to 3 percent of the total O_2 consumption.

REFERENCES

1. Kirklin JW, Archie JP Jr: The cardiovascular subsystem in surgical patients. Surg Gynecol Obstet 139:17-23, 1974

2. Sechzer PH, Wachtel J, Keats AS: Circulatory lability in myocardial stress in cardiovascular surgical patients. NY State J Med 69:2323-2328, 1969

3. Buckberg GD, Towers B, Phelia DE, et al: Subendocardial ischemia after cardiopulmonary bypass. J Thorac Cardiovasc Surg 64:669-684, 1972

4. Eger EI II, Smith NT, Stoelting RK, et al: Cardiovascular effects of halothane in man. Anesthesiology 32:396-409, 1970

5. Calverley RK, Smith NT, Prys-Roberts C, et al: Cardiovascular effects of prolonged enflurane anesthesia (abstract). American Society of Anesthesiologists, 1975, p 57

6. Kaplan JA, Miller ED, Bailey DR, et al: A comparative study of enflurane and halothane using systolic time intervals (abstract). American Society of Anesthesiologists, 1974, p 109

7. Stoelting RK, Reis RR, Longnecker DE: Hemodynamic responses to nitrous oxide-halothane and halothane in patients with valvular heart disease. Anesthesiology 37:430-435, 1975

8. Conahan TJ III, Ominsky AJ, Wollman HL: A prospective random comparison of halothane and morphine for open heart anesthesia. Anesthesiology 38:528-535, 1973

9. Kemmotsu O, Hashimoto Y, Shimosato S: The effects of fluroxene and enflurane on contractile performance of isolated papillary muscle from failing hearts. Anesthesiology 40:252-260, 1974

10. Mason DT: Regulation of cardiac performance in clinical heart disease. Am J Cardiol 32: 437-448, 1973

11. Eckberg DL, Drabinsky M, Braunwald E: Defective cardiac parasympathetic control in patients with heart disease. N Engl J Med 285:877-883, 1971

12. Chidsey CA, Braunwald E: Sympathetic activity and neurotransmitter depletion in congestive heart failure. Pharmacol Rev 18:685-700, 1966

13. Smith NT, Eger EI II, Stoelting RK, et al: The cardiovascular and sympathomimetic responses to the addition of nitrous oxide to halothane in man. Anesthesiology 32:410-421, 1970

14. Stoelting RK, Gibbs PS: Hemodynamic effects of morphine-nitrous oxide in valvular heart disease and coronary artery disease. Anesthesiology 38:45-52, 1973

15. Price HL: Myocardial depression by nitrous oxide and its reversal by calcium. Anesthesiology 44:211-215, 1976

16. Wong KC, Martin WE, Hornbein TF, et al: The cardiovascular effects of morphine sulphate with oxygen and with nitrous oxide in man. Anesthesiology 38:542-549, 1973

17. Lowenstein E, Hallowell P, Levine S: Cardiovascular response to large doses of intravenous morphine in man. N Engl J Med 281:1389-1393, 1969

18. Tweed WA, Minuck M, Mymin D: Circulatory responses to ketamine anesthesia. Anesthesiology 37:613-619, 1972

19. Traber DL, Wilson RD, Priano LL: A detailed study of the cardiopulmonary response to ketamine and its blockade by atropine. South Med J 63:1077-1081, 1970

20. Koriva DJ: Hemodynamic effects of intravenous ketamine in patients with coronary artery disease (abstract). American Society of Anesthesiologists 1974, p 233

21. Reves JG, Kravetz RA, McCracken LE, et al: Comparisons of morphine and ketamine anesthetic techniques for open heart surgery (abstract). American Society of Anesthesiologists, 1975, p 233

22. Stanley TH: Blood pressure and pulse rate responses to ketamine during general anesthesia. Anesthesiology 39:648-649, 1973

23. Price HL: Anesthesiology and circulatory homeostasis. Physiol Rev 40:187-218, 1960

24. Epstein JW, Hamilton WK, McCammond JM: The effect of thiopental on peripheral venous tone. Anesthesiology 22:525-528, 1961

25. Blackburn JP, Carway CM, Leigh JM, et al: The effects of anaesthetic induction agents upon myocardial contractility. Anaesthesia 26:93-94, 1971

26. Altura BT, Altura BM: Barbiturates and aortic and venous smooth-muscle function. Anesthesiology 43:432-444, 1975

27. Stanley TH, Bennett GM, Loeser EA, et al: Cardiovascular effects of diazepam and droperidol during morphine anesthesia. Anesthesiology 44:255-258, 1976

28. Benica JJ, Kennedy WF Jr, Ward RJ, et al: A comparison of the effects of high subarachnoid and peridural anaesthesia. Acta Anaesthesiol Scand Suppl 23:429-437, 1966

29. Kennedy WF Jr, Sawyer TK, Gerbenshagen HU, et al: Systemic cardiovascular and renal hemodynamic alterations during peridural anesthesia in normal man. Anesthesiology 31:414-421, 1969

30. Sagala JA, Ponka JL, Duvernoy WFC: Operative and nonoperative risks in the cardiac patient. J Am Geriatr Soc 12:529-534, 1975

31. Turhan S, Moffitt EA, Taylor WF, et al: Myocardial infarction after general anesthesia. JAMA 220:1451-1454, 1972

32. Abe FC, Goldberg MJ, Blair CS, et al: The influence of body temperature on early postoperative oxygen consumption. Surgery 60:85-92, 1966

33. Bay J, Nunn JF, Prys-Roberts C: Factors influencing arterial Po_2 during recovery from anaesthesia. Br J Anaesth 40:398-406, 1968

34. Carlsten A, Norlander O, Troell L: Observations on the postoperative circulation. Surg Gynecol Obstet 99:227-233, 1954

35. Marshall BE, Wyche MQ: Hypoxemia during and after anesthesia. Anesthesiology 37:178-209, 1972

36. Wilson RS, Sullivan SF, Malm JR, et al: The oxygen cost of breathing following anesthesia and cardiac surgery. Anesthesiology 39:387-393, 1973

Anesthesia for Patients with Heart Block and Artificial Cardiac Pacemakers

J. E. WYNANDS, MD*

MARCUS GERBEZIUS, of Germany, first described heart block in 1719. Lown and Kosowsky[1] have briefly traced the history of heart block and the various attempts to electrically stimulate the heart. The writings of Robert Adams, in 1826, and William Stokes, in 1846, firmly focused attention on the fact that a slow heart rate could produce apoplectic symptoms.

Callaghan and Bigelow,[2] in 1951, initiated the modern era of artificial cardiac pacing, while Chardack[3] developed the first fully implantable pacemaker in 1960. Since this development, great strides have been made. Electronic wizardry built into today's pacemakers has made anesthetizing a patient with heart block a relatively safe event.

Although special considerations must be given the patient with a pacemaker undergoing anesthesia, the problems presented by this situation are minor compared to those that may be encountered in the patient with heart block who does not have a pacemaker. To understand these problems, a brief review of heart block is necessary.

Heart Block.—The coordinated contractions of the atria and ventricles are accomplished by an impulse originating in the sinoatrial SA node and passing via 3 distinct pathways to the atrioventricular AV node, where the rate of propagation is slowed, the atria having contracted. The impulse then traverses the His-Purkinje system to initiate contraction of the ventricles. The His system consists of a common bundle which divides into right and left bundles. The left bundle then further subdivides into a left anterior superior fascicle and a left posterior inferior fascicle. Heart block may occur at any point in this pathway (fig 1).

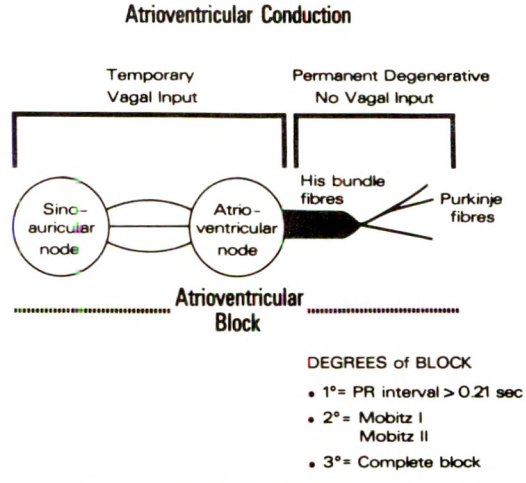


FIG 1. Atrioventricular Conduction.

When the block occurs either in the SA node, the internodal conducting system or the AV node, it tends to be of a temporary nature. Impulse formation in the SA node is greatly influenced by the level of vagal tone. Block occurring in the His-Purkinje system is termed infranodal block and is usually permanent and progressive. The His bundle electrogram[4] has made possible the precise location of the site of block in the His system and its correlation with events on the scalar electrocardiogram (ECG). Left axis deviation greater than minus 45° in the absence of an inferior infarct and pulmonary emphysema is indicative of left anterosuperior fascicle block.

Right axis deviation of plus 120° in the absence of an anterolateral infarct, pulmonary emphysema, and right ventricular hypertrophy is indicative of left posteroinferior fascicle block. This latter fascicle is anatomically the larger of the two and physiologically the more stable. Hearts that have

*Associate Professor, Department of Anesthesia McGill University, Senior Anesthetist, Royal Victoria Hospital, Montreal, Quebec, Canada.

right bundle branch block (RBBB) and left posterior fascicular block usually go on to trifascicular block. Only 10 percent of hearts with RBBB and left anterior fascicular block progress to trifascicular block. When left anterior and left posterior fascicular blocks occur together, the term left bundle branch block (LBBB) is used and is analogous to RBBB on the right side of the heart. RBBB may occur in normal hearts; LBBB is a serious finding.

First-degree heart block exists when the PR interval is greater than 0.21 sec. Second-degree heart block exists when some P waves are not followed by a QRS complex. Mobitz has subdivided 2nd-degree heart block into types I and II. Type I is characterized by a progressive lengthening of the PR interval prior to the dropping of the QRS complex. This is the classic Wenckebach phenomenon, where the block usually originates in the AV node conducting system and is reversible.

Mobitz type II heart block is characterized by a sudden dropping of a QRS complex, there having been no progressive lengthening in the PR interval. It is seen only when the block occurs in the His system and has a serious prognosis in that it frequently progresses to complete, or 3rd-degree, block. Third-degree block in the AV node is usually reversible whereas Mobitz type II block and 3rd-degree block of the His system are irreversible.

The QRS complex with 3rd-degree infranodal block is frequently wide and the ventricular rate is slow, averaging 40 bpm, although rates as slow as 15 bpm are encountered. Third-degree block of the AV node has a QRS complex of normal width and a faster rate (junctional rhythm). Complete infranodal heart block frequently results in a cardiac output which is not adequate for normal organ function. Congenital 3rd-degree heart block, because it is invariably high infranodal, is associated with a faster ventricular rate (50 bpm) which does not produce symptoms.[1,5-8]

The terms "sick sinus syndrome" and "brady-tachy" (bradycardia-tachycardia) syndrome refer to a group of rhythm disturbances resulting from failure of normal impulse formation in the SA node.[9-11] Rhythm disturbances may include (1) persistent severe sinus bradycardia; (2) intervals of sinus arrest as evidenced by absent P waves in which no escape rhythm arises or a lower ectopic pacemaker eventually takes over after several seconds; (3) paroxysmal or chronic atrial fibrillation due to temporary or permanent suppression of the sinus node; and (4) tachycardia alternating with bradycardia.[5]

TABLE 1
Common Causes of Heart Block

Organic
Primary conduction tissue
Lenègre's or Lev's disease
Disease affecting cardiac tissue in general
Ischemic heart disease; infarction
Cardiomyopathies
Myocarditis
Surgically produced
Congenital
Functional
Increased vagal tone
Drug therapy
Digitalis
Quinidine
Procainamide
Propranolol
K^+

Causes of Heart Block (table 1).—Heart block may occur at any age but is most commonly encountered in the 6th and 7th decades of life.[8,12] The commonest cause of heart block is a primary organic disruption of the His conduction system by Lenègre's or Lev's disease. The former is a sclerodegenerative process of the terminal portions of the fascicles and the latter is a fibrous encroachment of the proximal His conduction pathway from the fibrous structures surrounding it. These are the annuli of the mitral and tricuspid valves, the right fibrous trigone and the membranous portion of the interventricular septum. Similar primary degenerative changes may also involve the intra-atrial conduction system, producing a sick sinus syndrome.

The next commonest cause of heart block is coronary artery disease. The interruption of conduction may be due to a myocardial infarction or ischemia. The area and severity of heart block will depend upon the vessel affected. Involvement of the right coronary artery, which supplies the SA node in 55 percent of hearts, may temporarily produce SA node dysfunction on the basis of autonomic imbalance. A posteroinferior myocardial infarction will interfere with the blood supply to the AV node and frequently produce heart block which is usually transient.

TABLE 2
Indications for Pacing

SA node dysfunction
Brady-tachy syndrome
2° or 3° AV nodal block
Intermittent or fixed with slow ventricular response
Bifascicular or trifascicular block
RBBB and left anterior fascicle block
RBBB and left posterior fascicle block
Alternating LBBB and RBBB
LBBB and 1° heart block
↓ ↓
Stokes-Adams attacks
Angina
Heart failure
Ventricular irritability

It is not uncommon to find RBBB plus left anterior fascicular block with occlusion of the left anterior descending coronary artery. Trifascicular block on the basis of coronary artery occlusion implies massive muscle involvement which is usually not compatible with life.

Heart block is also frequently encountered with cardiomyopathies and myocarditis, and is well known in association with the surgical correction of congenital heart disease. These causes of heart block are organic in nature and generally permanent.

Other causes of heart block are functional and reversible. These include increased vagal tone and drug therapy with digitalis, quinidine, procainamide, propranolol and potassium. The vagus nerve has no effect on the infranodal conducting system whereas quinidine, procainamide, and propranolol depress conduction in the bundle of His.

Indications for Pacing (table 2).—Artificial pacemaker insertion is indicated when the patient has an impulse formation or conduction defect resulting in a heart rate and cardiac output that do not give adequate organ perfusion.[5,7,8,13,14] The reduction in heart rate is compensated for by an increase in stroke volume up to a maximum which will depend upon the state of health of the myocardium. In the face of a severely decreased cardiac output, blood pressure will be maintained by increasing peripheral resistance. When blood pressure falls, a point will be reached where organ failure will produce symptoms.

Heart block patients who have a history of Stokes-Adams attacks, angina, heart failure, or ventricular irritability are at great risk if subjected to general anesthesia,[15,16] which may precipitate heart block. General anesthesia also depresses myocardial function and peripheral resistance and, therefore, may cause organ failure in a patient who is barely compensating for his heart block.

Patients with bilateral fascicular block and a high degree of heart block who do not have symptoms are controversial.[5,7,14] The heart block, if originating in the AV node, may respond to atropine. Kastor[7] believes that patients with a type II 2nd-degree block should have a demand pacemaker even though they are asymptomatic.

Types of Pacemakers (table 3).—Fixed-rate pacemakers are ideal for patients with chronic complete heart block and a slow ventricular rate. Otherwise, a demand pacemaker should be employed; the ventricular-inhibited model is the most popular of these. The fixed-rate and the ventricular-inhibited demand pacemaker can be used with unipolar or bipolar leads via a transvenous or transthoracic approach. The most popular approach currently employed is transvenously through the cephalic vein in the deltopectoral groove.

Factors Affecting Pacing (table 4).—Alterations in the pacing threshold may markedly affect the performance of the pacing system. An increase in threshold may lead to intermittent or permanent failure of pacing. A decrease in threshold may induce ventricular fibrillation during the vulnerable period of the cardiac cycle. Normally, 30 ma current is required, and the standard pacemaker develops 10 ma. The threshold may be lowered to the point where the 10 ma current delivered by the battery is sufficient to induce ventricular fibrillation. Succinylcholine,[17] hyperkalemia,[17] and acid-base disturbances will raise the threshold. Hughes and coworkers[18] have reported an

TABLE 3
Types of Pacemakers

1.	Fixed-rate
2.	Demand
	Ventricular-inhibited
	Ventricular-synchronous
	Atrial-synchronous
	Atrial sequential ventricular-inhibited

TABLE 4
Common Factors Affecting the Pacing Threshold

↑	↓
Succinylcholine	Exercise
K^+↑ 4-7.1 mEq/L	Sympathomimetic amines
0.5-5 V	Hypoxia
Base excess: −15, +15	Ischemia
Sleep	Myocardial infarction
High threshold—Intermittent pacing	
Low threshold—Ventricular fibrillation	

increase in voltage requirements from 71 to 82 percent when the base excess was minus 15 and plus 15, respectively. Exercise, catecholamines, hypoxia, ischemia, and myocardial infarction reduce the pacing threshold.

Anesthesia for Pacemaker Implantation.—With this background, it is now appropriate to consider anesthesia for the implantation of a pacemaker, the change of a pacemaker battery, and for patients who have a pacemaker in place and are to undergo a surgical operation. It has been stated that heart block typically occurs in the 6th and 7th decades of life and the need for a pacemaker is dictated by symptom-producing heart block. These patients, because of their age, may have many associated diseases demanding specific considerations if morbidity and mortality are to be minimal. Their myocardial function may vary from bordering on normal to being barely compatible with life. The problems of assessing and anesthetizing a patient with severe heart disease will have been considered by other members of the panel.

A complete array of drugs and equipment must be at hand for cardiopulmonary resuscitation. The minimum requirements are a finger on the pulse, the ECG display on the oscilloscope, a DC cardiac defibrillator, and the usual drugs necessary for cardiac resuscitation.

Transvenous endocardial electrodes are most commonly employed with the implantation of a pacemaker. We, as others,[8,19] are firmly convinced that the electrodes should be inserted under local anesthesia. Patients who have heart block with symptoms and are submitted to general anesthesia are likely to develop cardiac standstill, ventricular tachycardia, or ventricular fibrillation.[15] Local anesthesia may be supplemented with light sedation. We use diazepam, finding that as little as 2.5 to 5 mg IV may be all that is required to calm the apprehensive patient.

It has been our experience that if the patient begins to object, the remedial action is not to increase sedation and thus verge on general anesthesia, but rather for the anesthesiologist to reassure the patient and have the surgeon stop the surgical procedure until adequate anesthesia at the operative site has been secured with the infiltration of additional local analgesic agent. We have found 0.5 percent lidocaine with epinephrine 1:200,000 ideal for this purpose.

This technic also makes possible creation of a pocket for the battery. The alternative is to secure pacing and then induce general anesthesia for the implantation of the battery, using a temporary external battery until the pocket is created and the implantable battery can be quickly secured to the leads and slipped into the pocket.

A thoracotomy is required for epicardial leads, which have been successfully implanted under local anesthesia and sedation.[20] We believe that such patients should have a temporary transvenous pacemaker inserted under local anesthesia, pacing secured, and the epicardial electrodes implanted under general anesthesia[21] appropriate for patients with cardiac disease, as discussed by other members of the panel.

Anesthesia for Battery Change.—A battery change is indicated when there is evidence of battery failure. In most instances, this is indicated by a slowing of the heart rate, which will signal complete failure of the battery in 7 to 20 days. Batteries may be elective ly changed just prior to the manufacturer's stated life expectancy of the battery. If the pacing system is functioning, the battery can be changed under general

anesthesia, recognizing that there is a critical point when the functioning battery is removed and the new battery secured to the leads and implanted into the pocket.

During this period the patient may revert to the rhythm for which he originally had the pacemaker inserted or cardiac standstill may occur. If the procedure is not quick and smooth, the heart, particularly in the presence of general anesthesia, may go into ventricular tachycardia or fibrillation. For these reasons, we believe batteries should be changed under local anesthesia with 0.5 percent lidocaine with epinephrine, 1:200,000, plus light sedation.

Anesthesia for Patients with Pacemakers. —Williams[5] stated that in 1974, 1/5000 North Americans were living with an implanted pacemaker. Johansson reports that in Sweden there are 63 new cases of complete heart block per million population per year.[17] It is obvious from these data that anesthesiologists will be increasingly faced by patients with pacemakers, and, from what has been said above, that the patient with heart block and symptoms is at much greater risk without a pacemaker than with one.

When the anesthesiologist is faced with a patient who has a pacemaker, we believe the procedure to be carried out should be as follows:

The reason for the implantation of the pacemaker should be known, as well as the type of pacemaker and its manufacturer's specifications.

It should be established that the pacemaker is functioning. This is achieved by monitoring the ECG, observing the pacemaker artifact, and assuring effective pacing. Failure of pacing may be due to battery failure, disruption of electrodes or failure of capture at a myocardial level (fig 2). A problem arises in a patient with a demand pacemaker of the ventricular-inhibited type when the patient's rhythm is such that the pacemaker is sensing the R wave but not having to initiate an impulse. The pacemaker should be converted with a magnet to a fixed-rate type and effective pacing assured.

Care must be taken to avoid trauma to the battery or damage to the leads. Transvenous pacemakers may be dislodged by placing the patient into an unusual position —for instance, hyperextending the arm of a patient with a temporary transvenous pacemaker placed through the brachial vein. This is also more likely to occur when the endocardial electrode has been in place for only a short time. The electrodes eventually become securely attached to the heart by endocardial reaction, but we have had patients whose electrodes became displaced as late as 2 weeks after implantation.

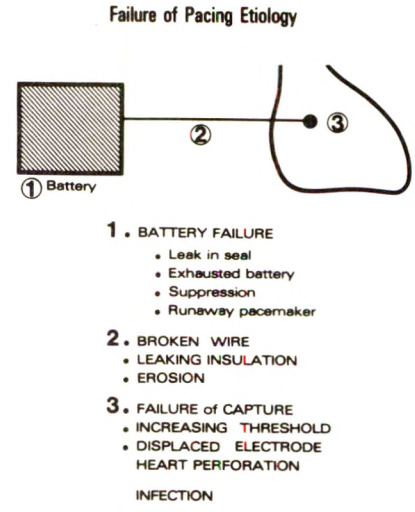


FIG 2. Failure of Pacing Etiology.

Factors which alter the pacing threshold, as described above, must be avoided. It must be emphasized that sudden reductions in cardiac output, as may occur with a massive hemorrhage or by suddenly taking the legs out of the lithotomy position, may result in myocardial ischemia and a lowered threshold. The adequacy of venous filling of the heart should be guaranteed.

Electrical Interference with Pacemakers. —Pacemakers may be adversely affected by electromagnetic fields.[17] These include cautery, diathermy, and radar impulses within physiologic range. In general, bipolar electrodes and fixed-rate pacemakers are less susceptible to electrical interference than unipolar leads and demand units.

Although there have been great technologic advances in the insulation of pacemakers, the grounding plate of the cautery should be placed as close to the operative site as possible and as far from the battery as possible. The cautery should not be used within 15 cm of the battery, not only because it may interfere with the battery circuitry, but also because if the cautery should come in contact with a break in the insulation of the electrode, the high-frequency current may cauterize the myocardium at the tip of the electrode, rendering it insensitive to pacing impulses.

When a situation exists that an electromagnetic field may be interfering with pacemaker function, the patient's hemodynamic stability must be monitored by following the pulse rate and blood pressure. If electrical interference occurs, the offending field must be turned off. If this is disadvantageous, as during a transurethral prostatic resection, the demand pacemaker should be converted to a fixed-rate unit, which may obviate the electrical interference from the cautery.

Inapparent signals from shortcircuits in the battery, from skeletal muscle, and from concealed premature ventricular contractions have been reported to interfere with demand pacemakers.[22] Outside the operating room, even microwave ovens and electric shavers may interfere with battery function.

The anesthesiologist with the above guarantees should then proceed to give an anesthetic best suited for the surgical requirements in view of the patient's medical status, knowing that the presence of the pacemaker is another factor adding to the safety of the patient with heart block during his operative and anesthetic experience.

CONCLUSIONS

A cardiac pacemaker is indicated when heart block results in Stokes-Adams attacks, heart failure, angina, or life-threatening ventricular arrhythmias. Heart block of this magnitude usually occurs in the 6th and 7th decades of life and is due to a degenerative process of the conducting system of the heart, although it is also seen earlier in life following myocardial infarction, myocardial inflammatory processes, and certain drug intoxications.

Because we are dealing with a geriatric population who may have associated diseases or with patients in a lower age group with severe myocardial disease, it is safest that temporary and permanent transvenous pacemakers be inserted under local anesthesia with appropriate sedation. A temporary transvenous pacemaker should be installed under local anesthesia prior to the implantation of a permanent transthoracic pacemaker under general anesthesia. When a pacemaker battery is to be changed, it can be safely and easily done under local anesthesia, again with appropriate sedation.

A patient with a pacemaker undergoing a surgical procedure is subject to various risks inherent to having a pacemaker. Patients with a fixed-rate pacemaker run the risk of sudden ventricular fibrillation if the pacemaker impulse falls in the vulnerable period of the cardiac cycle which corresponds to the upstroke of the T wave. Normally, 30 ma current is required to induce fibrillation during this period. This threshold will be markedly reduced by cardiac ischemia.

Patients with demand pacemakers may have their pacemakers suppressed by electromagnetic fields, the commonest cause being the cautery. This event can only be detected by monitoring the pulse, and fortunately the pacemaker usually resumes normal function as soon as the offending electromagnetic field is turned off.

Pacemaker failure may result in cardiac standstill, ventricular tachycardia, or ventricular fibrillation. In some instances, the pacemaker having been suppressed, the patient will revert to the heart rate for which the pacemaker therapy was instituted. In any event, all patients must be carefully monitored and all resuscitative drugs and procedures held in readiness should cardiovascular collapse be encountered following pacemaker failure.

REFERENCES

1. Lown B, Kosowsky BD: Artificial cardiac pacemakers (part I). N Engl J Med 283:907-916, 1970

2. Callaghan JE, Bigelow WG: An electrical artificial pacemaker for standstill of the heart. Ann Surg 134:8-17, 1951

3. Chardack WM, Gage AA, Greatbatch W: A transistorized, self-contained, implantable pacemaker for the long-term correction of complete heart block. Surgery 48:643-654, 1960

4. Scherlag BJ, Samet P, Helfant RH: His bundle electrogram. Circulation 46:601-613, 1972

5. Williams GD, Bulloch RT, Pearce MB, et al: Electric control of the heart/pacemakers, cardioversion and defibrillation (part I). Curr Probl Surg 3-67, Feb 1974

6. Kastor JA: Atrioventricular block (part I). N Engl J Med 292:462-464, 1975

7. Kastor JA: Atrioventricular block (part II). N Engl J Med 292:572-574, 1975

8. Sowton E, Hendrix G, Roy P: Ten-year survey of treatment with implanted cardiac pacemaker. Br Med J 3:155-159, 1974

9. Barrer MI: The sick sinus syndrome. Circulation 47:635-641, 1973

10. Rubenstein JJ, Schulman CL, Yurchak PM, et al: Clinical spectrum of the sick sinus syndrome. Circulation 46:5-13, 1972

11. Moss AJ, Davis RJ: Brady-tachy syndrome. Prog Cardiovasc Dis 16:439-453, 1974

12. McClish A, Benazera A, Lapointe P: Anesthesie legere a l'halothane pour implantation de cardiostimulateur. Union Med Can 103:853-860, 1974

13. Lown B, Kosowsky BD: Artificial cardiac pacemakers (part II). N Engl J Med 283:971-977, 1970

14. Rooney SM, Goldiner PL, Muss E: Relationship of right bundle-branch block and marked left axis deviation to complete heart block during general anesthesia. Anesthesiology 44:64-66, 1976

15. Wrigley FRH: Anaesthesia in Stokes-Adams disease. Can Anaesth Soc J 11:291-295, 1964

16. Vandam LD, McLemore GA Jr: Circulatory arrest in patients with complete heart block during anesthesia and surgery. Ann Intern Med 47:518-532, 1957

17. Scott DL: Cardiac pacemakers as an anaesthetic problem. Anaesthesia 25:87-104, 1970

18. Hughes HC Jr, Tyers GFO, Torman HA: Effects of acid-base imbalance on myocardial pacing thresholds. J Thorac Cardiovasc Surg 69:743-746, 1975

19. Lefemine AA: Cardiac pacemakers. Anesthesiology 27:843-857, 1966

20. Guharay BN, Saha AK, Mittra D, et al: Epicardial electrode implantation on both right and left ventricles using local anaesthesia. Br J Surg 61:878-883, 1974

21. Dixon SH Jr, Perryman RA, Morris JJ Jr, et al: Transmediastinal permanent ventricular pacing. Ann Thorac Surg 14:206-213, 1972

22. Barold SS: Inapparent signals to demand pacemakers. Chest 63:467-468, 1973

ROUTINE PHENOBARBITAL. Phenobarbital may increase the activity of glucuronyl transferase and facilitate the production of water-soluble bilirubin. Administration of this drug prenatally may reduce the incidence of neonatal hyperbilirubinemia. Starting at 36 weeks gestation, 221 prenatal patients received oral phenobarbital 16 mg 4 times daily. Serum bilirubin levels exceeded 10 mg/dl in 4.1 percent of infants exposed to phenobarbital before birth. In contrast, serum bilirubin exceeded this level in 16.3 percent of infants not exposed to phenobarbital. Routine phenobarbital therapy may be a safe and effective method of preventing neonatal hyperbilirubinemia. *(Thomas CR: Routine phenobarbital for prevention of neonatal hyperbilirubinemia. Obst Gyn 47:304-308, 1976)*

Drugs in Cardiac Supportive Care

ROGER D. WHITE, MD*

IT IS essential to consider several basic principles of drug therapy when one elects to use drugs in any situation. This has critical implications in patients with cardiac disease. Some of the questions to be answered are: What is the precise indication for drug intervention? Which drug is most appropriate? What are the possible or likely side effects? Does drug therapy carry a risk of adverse effect that might, in fact, worsen the situation?

This presentation is directed at emergencies, or potential emergencies, for which drug treatment might be considered life-saving. As such, it falls within the province of resuscitation and emergency cardiac care. Objectives of intervention with drugs in this context include: to slow or to accelerate cardiac rate; to suppress ventricular ectopic activity; to stimulate spontaneous or more forceful myocardial contractions; to increase perfusion pressure; to correct metabolic acidosis.

The use of drugs in emergency cardiac care is discussed within the framework of several clinical situations in which urgent drug therapy is indicated. Specific drugs that are useful, and even essential, in emergency management include digoxin (or other rapid-acting digitalis glycosides), propranolol, atropine, lidocaine, procainamide, isoproterenol, epinephrine, calcium chloride ($CaCl_2$), and sodium bicarbonate ($NaHCO_3$).

The Need for a Planned Approach.—Unfortunately, in the presence of life-threatening crises, it is almost never possible to take time to ask and to answer all questions. Physicians involved in the management of patients with life-threatening crises, therefore, must have a well-planned and organized approach to such events in advance of their occurrence. This discussion will attempt to develop such an approach to several potentially life-threatening problems in patients with cardiac disease. The orientation is deliberately practical, without details of the theoretic considerations that underlie both the problems and their management. Furthermore, since "cardiac disease" encompasses a whole spectrum of lesions and related complications, primary consideration will be directed toward patients with coronary artery disease.

It must be emphasized that before the approach outlined herein is applied, all other factors in the anesthetic circumstance which might be causing or contributing to the apparent complication must be ruled out. These include, among others, inadequate ventilation, too light or too deep anesthesia, and electrolyte imbalance. The assumption that these have been considered will be made throughout this discussion.

Some of the questions to be reviewed are these: What circumstances might necessitate prompt drug intervention? In those circumstances, what specific indicators are there for drug treatment? What are the appropriate drugs and doses? What side-effects might be anticipated? These questions will be considered in the context of some of the potentially life-threatening conditions that may suddenly develop in patients with cardiac disease under anesthesia, particularly in patients with coronary artery disease.

The following outline will be used to identify conditions that might necessitate rapid intervention with drug therapy:

I. Cardiac dysrhythmias
   - A. Supraventricular
     1. Bradydysrhythmias—sinus or junctional
     2. Tachydysrhythmias — atrial flutter, atrial fibrillation, paroxysmal atrial tachycardia
   - B. Ventricular
     1. Ventricular premature beats (VPBs)
     2. Ventricular tachycardia
     3. Ventricular fibrillation

*Assistant Professor of Anesthesiology, Mayo Medical School, Rochester, Minnesota 55901.

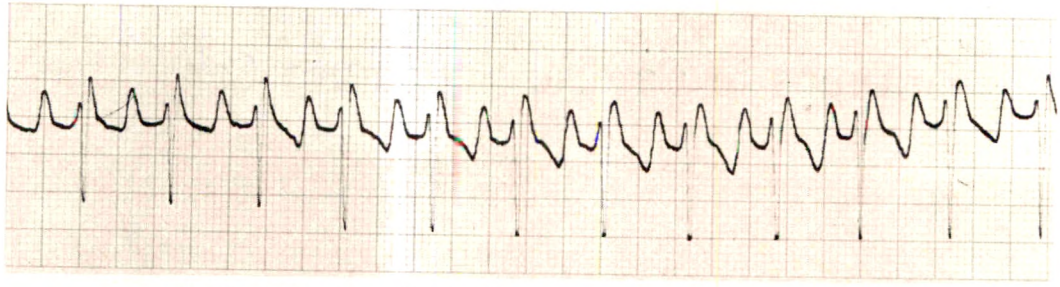


FIG 1. Atrial flutter with 2:1 A-V conduction. Ventricular rate 130 bpm.

FIG 2. Atrial fibrillation with rapid ventricular response. Ventricular rate approximately 160 bpm.

C. Atrioventricular (A-V) block
   1. Second-degree (Mobitz I and II)
   2. Third-degree (complete heart block)

II. Acute hypotension or hypertension

III. Cardiopulmonary arrest

I. Cardiac Dysrhythmias.

A. Supraventricular. 1. Bradydysrhythmias—Sinus or Junctional.—Slowing of the heart rate as an apparent result of reflex vagal activity during a surgical procedure is well known to anesthesiologists. The cardiac vagolytic action of atropine predictably produces an increase in the rate. Because heart rate is a major determinant of myocardial O_2 requirement,[1] acceleration of the rate in patients with coronary artery disease may disturb the relationship between myocardial O_2 supply and demand, leading to acute myocardial ischemia.[2]

Supraventricular bradycardia that does not compromise cardiac output or permit ventricular escape ectopy usually does not require treatment. If, however, bradycardia is accompanied by hypotension or frequent ventricular ectopic escape beats, treatment is necessary. Atropine can be given IV in increments of 0.3 to 0.5 mg until the desired rate is attained (usually around 60 to 70 bpm).

2. Tachydysrhythmias. — Atrial flutter (fig 1) may become life-threatening if the ventricular response is rapid enough to produce an acute fall in cardiac output and is accompanied by hypotension. In addition to the rapid ventricular rate, the myocardial O_2 requirement is increased and the coronary flow is compromised by the abbreviated diastolic time. This applies to rapid ventricular rates in all tachydysrhythmias and is a major reason why tachydysrhythmias may be poorly tolerated in the presence of coronary artery disease.

Atrial flutter is usually sensitive to direct-current (DC) cardioversion, which is the treatment of choice when possible. If impossible, and if hemodynamic deterioration is present, rapid digitalization should be carried out. Digoxin (0.5 to 0.75 mg) should be given IV, then 0.25 mg every 4 to 6 hours until the ventricular rate is controlled. If the ventricular rate is poorly controlled by digitalis, propranolol in 0.5-mg increments up to 3 mg can be given IV, slowly and cautiously. Congestive cardiac failure and pulmonary disease with a bronchospastic component are contraindications to propranolol. It must be kept in mind that acute congestive failure may be *precipitated* by the rapid ventricular rate.

In general, the same principles apply to the acute management of atrial fibrillation with a rapid ventricular rate (fig 2) and paroxysmal atrial tachycardia (fig 3). If hemodynamic deterioration develops rapidly after onset of these dysrhythmias, DC cardioversion should be employed when

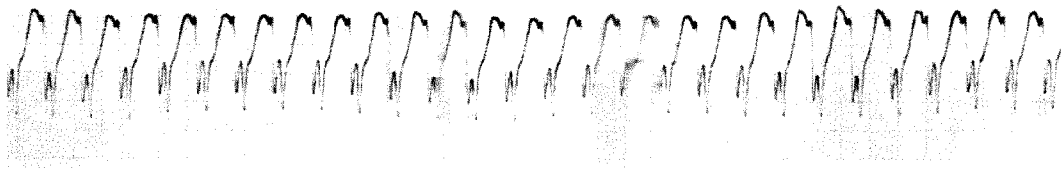


FIG 3. Paroxysmal atrial tachycardia in patient with known Wolff-Parkinson-White syndrome. Ventricular rate 220 bpm. Hemodynamic deterioration necessitated immediate DC cardioversion.

available. Otherwise, rapid digitalization is necessary to control the ventricular rate.

B. Ventricular. 1. Ventricular Premature Beats.—Ventricular ectopic activity, whether due to enhanced automaticity or reentry,[3] may be electric evidence of acute myocardial ischemia.[4] The probable role of the slow response action potential (the slow inward current) in the genesis and maintenance of reentrant dysrhythmias has recently been reviewed.[5] It is likely that the slow response action potential accounts for much of the ectopy seen in the early phase of acute myocardial ischemia.[6]

When ischemia is likely to be the cause of dysrhythmias, prompt pharmacologic suppression is usually necessary, since ventricular ectopic activity may progress rapidly to ventricular tachycardia or ventricular fibrillation (VF) or both. VPBs that are frequent (>5/min), multiform, close coupled (near the apex of the preceding T wave), or recurring in bursts or salvos of two or more in succession generally are considered specific indications for drug suppression[7] (fig 4). The drug of choice in such circumstances is lidocaine. A bolus of 75 to 100 mg (1 mg/kg) can be given IV and repeated PRN every 3 to 5 minutes up to a total of about 300 mg.[8] In order to sustain the plasma level of lidocaine in a suppressive range (1.5 to 5.5 μg/ml) it is necessary to follow the bolus with a continuous infusion of lidocaine at 1 to 4 mg/min.[9] This can be done by adding 1 gm of lidocaine to 250 ml of 5 percent dextrose in water (D/W) (4 mg/ml lidocaine) and infusing the solution via a

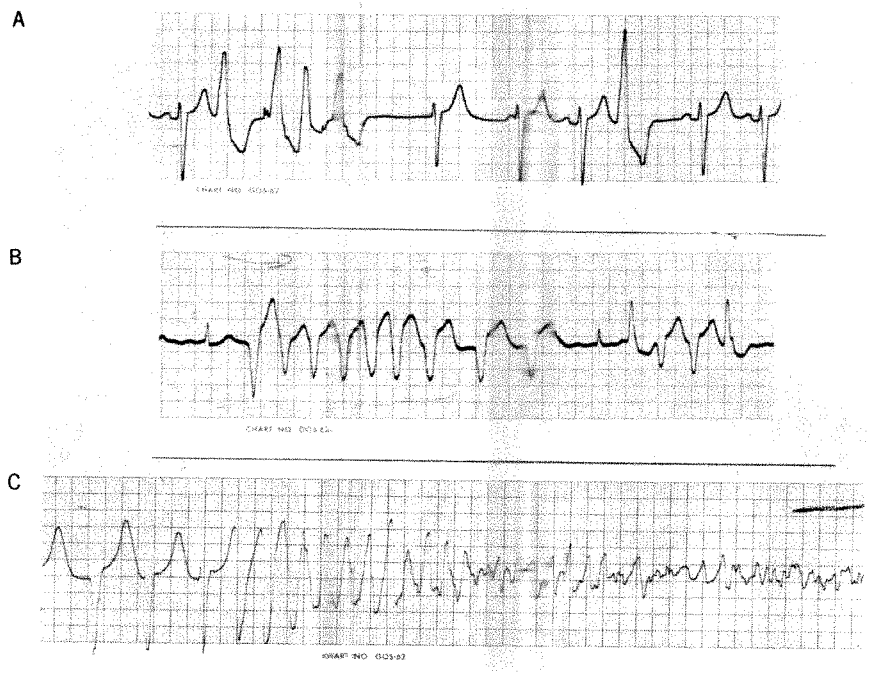


FIG 4. A. Ventricular ectopy, with run of 4 successive VPBs on left, followed by junctional escape beat. B. Burst of ventricular tachycardia. C. Brief burst of ventricular tachycardia initiated by close-coupled VPB (4th beat from left) with rapid degeneration into VF.

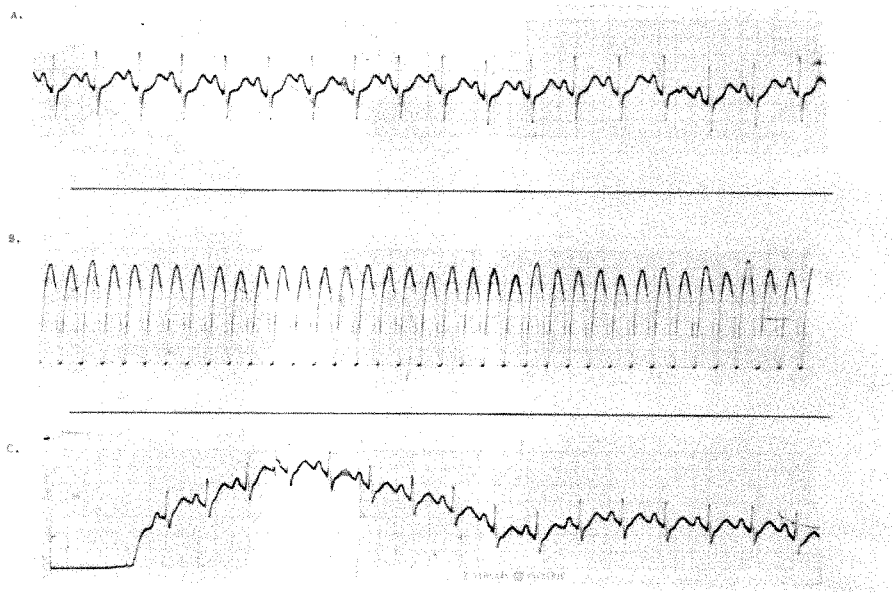


FIG 5. Sequential tracings in 50-year-old man with triple-vessel coronary artery disease undergoing anesthesia and surgery. A. Before induction: sinus tachycardia, 115 bpm. B. Prior to draping, while receiving halothane-N_2O-O_2: ventricular tachycardia, 250 bpm. Systolic pressure 50 torr. C. Immediately after 100 mg lidocaine IV and 200 watt-seconds DC countershock: sinus tachycardia, 120 bpm.

microdrip apparatus, initially at 60 microdrops/min (4 mg/min).

Lidocaine undergoes hepatic degradation. If cardiac output and hepatic blood flow are impaired or if hepatic disease is present, lidocaine toxicity will develop if the dose is not reduced. Plasma levels of lidocaine in excess of 6 μg/ml are likely to be associated with toxicity, usually related to the central nervous system.[7]

If lidocaine is ineffective in suppressing the ectopy, as may infrequently be the case,[10] procainamide can be used. It is given IV at a rate of 25 to 50 mg/min until adverse reactions occur, the dysrhythmia is terminated, or a total dose of 1 gm is given.[11] The ECG and the blood pressure must be observed closely, since procainamide may produce hypotension and ECG changes indicative of toxicity, usually widening of the QRS interval. Given in this manner, it can be used safely and effectively to suppress lidocaine-resistant ventricular ectopy.

2. Ventricular tachycardia (fig 5) can produce a precipitous decrease in cardiac output and blood pressure—even frank cardiopulmonary arrest. In such cases, *immediate* DC cardioversion is the treatment of choice, followed by injection of lidocaine as a bolus and by infusion as just described. If hemodynamic deterioration is not present, lidocaine as a bolus and an immediate infusion can be given. If this treatment does not cause the rhythm to improve promptly, DC cardioversion should be used, since ventricular tachycardia may rapidly degenerate into VF.

3. Ventricular fibrillation is a lethal dysrhythmia. Immediate treatment is DC defibrillation, followed by an injection of lidocaine as a bolus of 75 to 100 mg and an infusion at 1 to 4 mg/min. It must be emphasized that in the presence of myocardial ischemia, both ventricular tachycardia and VF, if terminated by DC countershock, must be followed by lidocaine therapy in order to maintain suppression of the ventricular ectopy and to prevent recurrence of the dysrhythmias.[7]

C. Atrioventricular Block.—As first-degree A-V block is not a life-threatening disorder, it will not be discussed here.

1. Second-degree block is classified as Mobitz I and Mobitz II. Mobitz I block is of the Wenckebach type, in which there is progressive lengthening of the P-R interval before the dropped ventricular response. This form of block, which is almost always at the junctional level, may accompany acute myocardial infarction of the inferior wall.[12] No treatment is usually required, since the ventricular rate is adequate, even if complete block should develop (the A-V

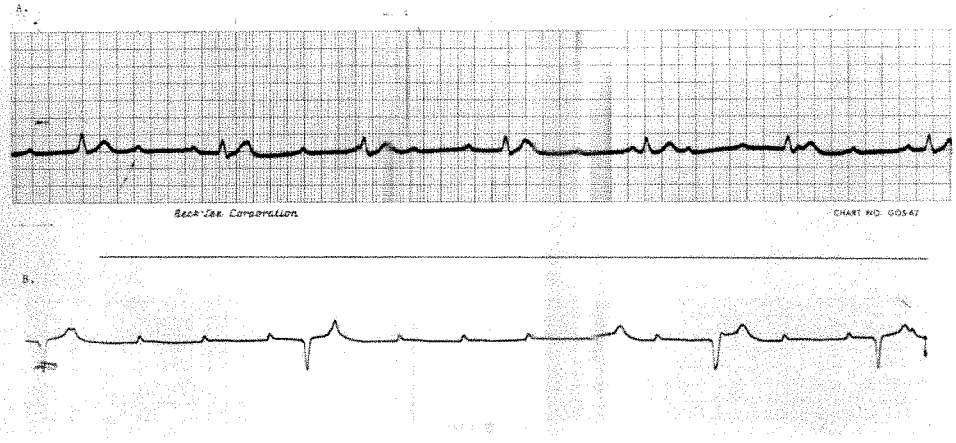


FIG 6. Complete A-V block. A. Atrial rate 90 bpm; ventricular rate 36 bpm. B. Atrial rate 77 bpm; ventricular rate variable, 25 to 30 bpm.

junction is usually the escape pacemaker in such cases). If the ventricular rate is associated with hypotension, atropine can be used in increments of 0.3 to 0.5 mg.

In Mobitz II A-V block, dropped beats occur, but the P-R interval of all conducted beats is constant. The conduction defect is below the A-V node, and in most cases there is some degree of bilateral bundle branch block.[12] Should this form of block develop, transvenous pacing is indicated, since progression to complete heart block will be accompanied by unusually slow ventricular rates of 30 to 40 bpm. Attempting to accelerate the ventricular rate with atropine or isoproterenol may slow the ventricular rate by increasing the degree of block.[13]

2. Third-degree A-V block (complete heart block) (fig 6) is usually accompanied by idioventricular escape rates of 30 to 40 bpm. Definitive treatment is cardiac pacing; this should be accomplished as soon as possible. It may be necessary to sustain the ventricular rate while preparations for pacing are made; atropine in increments up to a total of 2 mg can be tried. An infusion of isoproterenol is more likely to be effective. For this, 1 mg of isoproterenol can be added to 250 ml of 5 percent D/W, and this solution can be infused via microdrip until a sufficient ventricular rate is attained, usually 50 to 60 bpm.

II. Acute Hypotension or Hypertension.— The fundamental problem developing from either hypotension or hypertension in patients with coronary artery disease relates to an acute imbalance between myocardial O_2 supply and demand. Hypotension, by reducing pressure-dependent coronary blood flow, can produce acute myocardial ischemia, and the patient must be treated promptly. Hypertension, by increasing left ventricular wall tension, a major determinant of O_2 requirement, can increase myocardial O_2 demand. In the anesthetized patient, the initial evidence of acute myocardial ischemia produced by either hypotension or hypertension is S-T-T wave displacement or inversion on the ECG. Almost always the cause can be identified and appropriate treatment can be instigated. For example, acute and severe hypertension and tachycardia may accompany and follow laryngoscopy and intubation if anesthetic depth is insufficient. If this occurs, prompt control usually can be achieved by administration of anesthetic agents.

If hypotension is a manifestation of acute pump failure, vasoactive drug support may be necessary. Dopamine is useful in this circumstance,[14] and 200 mg is added to 250 ml of 5 percent D/W. Initially 2.5 μg/kg/min can be infused via microdrip and increased or decreased according to response.

Sodium nitroprusside is a relatively recent addition to drug alternatives in supportive cardiac care.[15] It is useful in the control of hypertensive crises, but it may also be employed in acute left ventricular failure accompanying myocardial infarction, because of its systolic unloading effect (a reduction in left ventricular afterload).[15,16] It is given as a constant IV infusion from a dilution of 50 mg in 500 ml of 5 percent D/W. The infusion can be started at 0.5 μg/kg/min and adjusted according to response.

These are only two of the pharmacologic options available in the presence of hypotension or hypertension. It is apparent that the cardiac origin of the crisis needs to be clearly established before such therapy is employed. If acute cardiac failure is present, hemodynamic monitoring should include direct arterial and pulmonary capillary wedge pressure as soon as feasible.

III. Cardiopulmonary Arrest. — Cardiopulmonary arrest may result from VF (or pulseless ventricular tachycardia), ventricular asystole (standstill), or cardiovascular collapse (electromechanical dissociation). Proper management of cardiopulmonary arrest necessitates a knowledge of, and performance ability in, both basic and advanced cardiac life support.[17] The specifics of advanced treatment modalities are reported by the American Heart Association.[18]

Ventilation with 100 percent O_2 must be instituted as soon as possible, for reasons well known to anesthesiologists. They include low cardiac output during cardiopulmonary resuscitation and intrapulmonary shunting, both major causes of hypoxemia.

Metabolic acidosis, the inevitable accompaniment of the arrested state, is treated with $NaHCO_3$, ideally with measurement of arterial blood-gas tension and pH as guides to therapy. Empirically, 1 mEq/kg can be given initially and repeated once if necessary. Thereafter, one-half the initial dose is given. Metabolic alkalosis, hyperosmolality, and retention of Na^+ and H_2O are possible consequences of administration of excessive $NaHCO_3$.

Ventricular fibrillation, as already pointed out, is best treated promptly by DC defibrillation, followed by lidocaine. If the fibrillation is fine, it can be converted to a coarse fibrillation more responsive to countershock by giving IV 0.5 mg (5 ml 1:10,000) of epinephrine. This can be repeated every 5 minutes, if needed. The patient with coarse VF that is unresponsive to defibrillation or that reverts repeatedly after temporary conversion should be treated with lidocaine as both bolus and infusion. If refractory VF persists, propranolol in 1-mg increments, along with 1.2 to 2.4 mg of atropine, can be given.[19] The total dose of propranolol probably should not exceed 3 to 5 mg. Hypoxemia and metabolic acidosis must be corrected before defibrillation can be expected.

Ventricular standstill is the most ominous form of arrest. After oxygenation and treatment for metabolic acidosis, 0.5 mg of epinephrine or 250 to 500 mg (10% solution) of $CaCl_2$, or both, can be tried. These can be repeated, or isoproterenol as an infusion can be begun.

Electromechanical dissociation is best treated with $CaCl_2$ in the foregoing doses to improve the cardiac inotropic state and, hence, cardiac output. If calcium is ineffective, epinephrine can be added. Hypoxemia and metabolic acidosis must be corrected before results can be expected in any of these causes of arrest.

REFERENCES

1. Braunwald E: Control of myocardial oxygen consumption: physiologic and clinical considerations. Am J Cardiol 27:416-432, 1971

2. Richman S: Adverse effect of atropine during myocardial infarction: enhancement of ischemia following intravenously administered atropine. JAMA 228:1414-1416, 1974

3. Moe GK, Mendez C: Physiologic basis of premature beats and sustained tachycardias. N Engl J Med 288:250-254, 1973

4. Wit AL, Bigger JT Jr: Possible electrophysiological mechanisms for lethal arrhythmias accompanying myocardial ischemia and infarction. Circulation 52 (suppl 3):96-115, 1975

5. Cranefield PF: The Conduction of the Cardiac Impulse: the Slow Response and Cardiac Arrhythmias. Mount Kisco, New York, Futura Publishing Company, 1975

6. Wit AL, Friedman PL: Basis for ventricular arrhythmias accompanying myocardial infarction: alterations in electrical activity of ventricular muscle and Purkinje fibers after coronary artery occlusion. Arch Intern Med 135:459-472, 1975

7. Collinsworth KA, Kalman SM, Harrison DC: The clinical pharmacology of lidocaine as an antiarrhythmic drug. Circulation 50:1217-1230, 1974

8. Rosen MR, Hoffman BF, Wit AL: Electrophysiology and pharmacology of cardiac arrhythmias. V. Cardiac antiarrhythmic effects of lidocaine. Am Heart J 89:526-536, 1975

9. Harrison DC: Practical guidelines for the use of lidocaine: prevention and treatment of cardiac arrhythmias. JAMA 233:1202-1204, 1975

10. Alderman EL, Kerber RE, Harrison DC: Evaluation of lidocaine resistance in man using intermittent large-dose infusion techniques. Am J Cardiol 34:342-349, 1974

11. Winkle RA, Glantz SA, Harrison DC: Pharmacologic therapy of ventricular arrhythmias. Am J Cardiol 36:629-650, 1975

12. Merideth J, Pruitt RD: Cardiac arrhythmias. 5. Disturbances in cardiac conduction and their management. Circulation 47:1098-1107, 1973

13. Danzig R, Alpern H, Swan HJC: The significance of atrial rate in patients with atrioventricular conduction abnormalities complicating

acute myocardial infarction. Am J Cardiol 24:707-712, 1969

14. Holzer J, Karliner JS, O'Rourke RA, et al: Effectiveness of dopamine in patients with cardiogenic shock. Am J Cardiol 32:79-84, 1973

15. Palmer RF, Lasseter KC: Drug therapy: sodium nitroprusside. N Engl J Med 292:294-297, 1975

16. Parmley WW, Chatterjee K, Charuz Y, et al: Hemodynamic effects of noninvasive systolic unloading (nitroprusside) and diastolic augmentation (external counterpulsation) in patients with acute myocardial infarction. Am J Cardiol 33:819-825, 1974

17. American Heart Association and National Academy of Sciences-National Research Council: Standards for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). JAMA 227 (suppl):833-868, 1974

18. American Heart Association: Advanced Cardiac Life Support. Dallas, American Heart Association, 1975

19. Sleman G, Stannard M: Beta-adrenergic blockade and cardiac arrhythmias. Br Med J 4:508-512, 1967

RATE-PRESSURE PRODUCT. The product of heart rate and systolic blood pressure correlates with myocardial oxygen requirements. The constancy of this product during right atrial pacing induced anginal pain with or without angiotension produced hypertension was studied in 12 patients. Without angiotension produced elevations in blood pressure angina occurred at a heart rate of 100 beats/min and a systolic blood pressure of 139 torr. When systolic blood pressure was increased to 176 torr angina occurred when the cardiac rate was 131 beats/min. Despite the differences in rate and pressure the resulting rate-pressure product at which angina occurred was similar with or without hypertension. These data support the hypothesis that there is a constant myocardial oxygen consumption for each patient at which angina develops regardless of whether there is a relatively greater increase in heart rate or blood pressure. In contrast, drugs may change the angina threshold. For example patients exercising after nitroglycerin develop angina at a higher rate-pressure product while after propranolol the product at the onset of angina may be reduced. *(Cokkinos DV, Voridis EM: Constancy of pressure-rate product in pacing-induced angina pectoris. Brit Ht J 38:39-42, 1976)*

Anesthesia for Patients Early After Infarction

EMERSON A. MOFFITT, MD*

FOR an elective operation, sound advice, from Tarhan's study,[1] is to wait at least 6 months after a myocardial infarction (table). Tarhan's group documented the incidence of reinfarction occurring within a week of operation as 37 percent for patients anesthetized within 3 months of infarction. Waiting 3 to 6 months after infarction before operation reduced the incidence to 16 percent. The incidence of postoperative reinfarction stabilized at 5 percent after a 6-month interval from the previous infarction. The period of highest risk of anesthesia and operation is the first 15 days after infarction, with the new segment of dead and ischemic muscle present.

Everyone practicing clinical anesthesia has been, or sometime will be, faced with the necessity of anesthetizing a patient within 6 months of infarction. While only life-threatening emergencies should be operated upon early after infarction, they do occur and operation must be done. Other than the rare occurrence of appendicitis or a strangulated hernia, the most likely true emergency early after infarction is embolectomy. A pulmonary embolus may require whole body perfusion for removal: an anesthetic challenge of great magnitude. More likely is a clot from the left atrium, occluding a regional artery. An embolus to a femoral or brachial artery can be quite simply removed, but if infarction of bowel occurs from a mesenteric arterial embolus, a more major anesthetic procedure is required, with a much higher risk.

A. *Preoperative Assessment.*

The major areas for assessment include:

(a) *Circulatory.* Here is the site of the problem: the weakened myocardium. How reduced is peripheral blood flow? Are the limbs dusky and cool? Is there frank congestive failure? Is there hypotension, with or without vasoconstriction? Is there a slow or fast pulse rate or arrhythmias? Is urinary output adequate?

(b) *Respiratory.* Has the patient dyspnea or hypoxemia, with or without an increased inspired O_2 concentration? Does he need assistance with ventilation?

(c) *Laboratory work.* Are hematocrit,

TABLE

Myocardial Infarction After General Anesthesia: Relation to Interval from Previous MI to Surgery, by Sex[1]

Months	MI in men (M)		MI in women (W)		Percent MI again (M + W)
	Previously	Again postop	Previously	Again postop	
0-3	8	3			37
4-6	15	3	4		16
7-12	31	2	11		5
13-18	26	1	1		4
19-24	19	1	2		5
25+	186	10	46	1	5
Old MI, age not recorded	64	7	9		10
Total	349	27	73	1	6.6

*Professor and Head, Department of Anaesthesia, Faculty of Medicine, Dalhousie University, Halifax, Canada.

clotting factors, and electrolytes normal? Has he been taking anticoagulants? Is whole blood available and cross-matched?

(d) *Drugs.* These patients may be on a variety of cardiosupportive drugs, from digitalis, diuretics, propranolol and lidocaine to the catecholamines by drip.

One can readily see that the more affirmative answers there are to the above questions, the greater the risk of anesthesia and operation.

B. *Electrocardiographic Picture of Acute Infarction.*

Three zones in the region of an infarct are involved:

(a) A peripheral zone of ischemia causes inversion of the T wave due to altered repolarization.

(b) Next, a zone of muscle injury causes elevation of the S-T segment.

(c) The central zone of infarction, or death of muscle, causes Q or Q-S waves, due to absence of a depolarizing current from the dead tissue, plus opposing currents from other parts of the heart.

During recovery from the infarct (the subacute and chronic stages), the S-T segment is often the first to return to normal, then the T wave, due to disappearance of the zones of injury and ischemia.

C. *Basic Rules for Anesthetic Management.*

The paramount necessity is to maintain the already precarious circulation. The principles are:

(a) Use as light a level as is possible for the particular operation. Often, only analgesia and amnesia are needed, or regional anesthesia.

(b) Many combinations of drugs are possible, and can be used safely in small, careful doses.

(c) Assure an elevated inspired O_2 concentration and adequate ventilation.

(d) Keep the blood volume optimal: replace losses early.

(e) Treat abnormalities of rate and rhythm vigorously.

(f) Monitor closely.

D. *Effects of Anesthetic Drugs.*

All the potent agents depress myocardial contractility and dilate the peripheral vascular bed in direct relation to their concentration in arterial blood. The inhaled gases do this in the decreasing order of: halothane, methoxyflurane, enflurane, and N_2O. However, the risk of hypoxemia is incurred in using N_2O in the patient with a precarious circulation.

The opiates and Innovar® do not depress the myocardium particularly, but by arteriolar dilation they can produce hypotension in a vasoconstricted patient. Several drugs often given to these patients, such as lidocaine, quinidine, and diphenylhydantoin, can prolong the action of tubocurarine.

E. *Anesthetic Technics.*

The best approach depends on the site and kind of operation, as well as the length of time after the infarction.

The myocardium is most easily depressed during the first 30 postinfarction days. This early period also has the greatest likelihood of thrombus formation in the left atrium, requiring peripheral embolectomy. For the latter, local infiltration, small doses of diazepam and opiates, plus O_2 by mask, usually suffice.

The circulation is more stable after the 1st month. Then more safe choices are available:

(a) Careful induction with diazepam or thiopental.

(b) N_2O and O_2 plus opiate or small amounts of enflurane.

(c) Spontaneous or controlled breathing, as required.

F. *Potential Problems.*

The circulatory problems encountered during anesthesia are generally of 3 kinds:

(a) Abnormal rate, usually bradycardia.

(b) Abnormal rhythm; may be due to: damage to the conduction system; ectopic beats; effect of anesthetic agents.

(c) Decreased left ventricular function.

G. *Bradycardia.*

A heart rate below 60 bpm in origin may be:

(a) Extracardiac: due to vagal reflex.

(b) Intracardiac: in a posterior infarction, vagal reflex or damage to the conducting system.

(c) Iatrogenic: (1) From drugs such as digitalis and propranolol; (2) From anesthetic agents, the most potent of which slow the heart rate.

The hazard of bradycardia is that cardiac output further decreases. Due to the area of injured myocardium, the heart cannot increase its stroke volume to make up for fewer strokes. Also, during the long diastole, ectopic foci fire off from the area of the infarct. With these ectopic foci and the regular pacemaker both firing, there is the risk of ventricular fibrillation, due to an ectopic contraction hitting a T wave.

Sinus bradycardia may be abolished by small, repeated doses of atropine. Blocking vagal depression of contractility allows increase of sympathetic tone to the heart and greater cardiac output by this second mechanism, along with increase in rate.

With severe bradycardia or heart block present before anesthesia, the best approach is to have a transvenous pacemaker inserted for control of the rate.

During anesthesia, maintain normocardia and an elevated inspired O_2 concentration. Both gallamine and pancuronium tend to increase heart rate.

H. *Arrhythmias.*

The potential causes of, and contributors to, ectopic activity early after an infarction are many. Several are often present together:

(a) Reduced Pao_2 from respiratory or circulatory causes.

(b) Ectopic foci in ischemic and dead tissue areas, engendered by altered electrical activity.

(c) Hyper- and hypocapnea.

(d) Hyper- and hypokalemia.

(e) Catecholamine increase, either endogenous or exogenous.

(f) Digitalis toxicity and high doses of quinidine.

Digitalis is required for rapid atrial fibrillation, while both ventricular tachycardia and fibrillation require cardioversion.

The ventricular-hyperirritability rhythms (ectopic beats and bigemini) should be treated early and vigorously. Eliminate the possibilities of high or low $Paco_2$ and low Pao_2. If total body K^+ is reduced, 2 to 4 mEq boluses of KCl usually abolish premature ventricular contractions. Follow with KCl by drip. Lidocaine (in the doses mentioned by Dr. White[2]) is the traditional agent. These patients, already anesthetized and probably with a reduced cardiac output, are poor candidates for propranolol. Pace the heart at a faster rate if a pacemaker catheter is in place.

I. *Decreased Ventricular Function.*

Arterial hypotension is the most dreaded happening during anesthesia early after infarction, since above all, coronary perfusion must be maintained in the presence of a damaged myocardium. One must decide upon the causes of the reduced ventricular function. Has the pump failed or are other factors contributing to the inadequate circulation? Is congestive failure present, with high central venous, pulmonary arterial, and left ventricular end-diastolic pressure (LVEDP)? Are there signs of pulmonary edema, hypoxemia, or severe peripheral vasoconstriction?

The key to successful treatment of low cardiac output is to decide whether left atrial pressure and LVEDP are low, normal, or high. If they are low or normal, increasing the blood volume will raise these pressures and increase stroke volume and cardiac output. Starling's law works, with an increase of LVEDP improving cardiac output by sarcomere stretching, up to an LVEDP of 20 to 22 torr. Above that pressure, the sarcomeres are overstretched and the ventricle begins to dilate and fail. Since central venous pressure is an imprecise indicator of LVEDP, one must either measure pulmonary wedge pressure by Swan-Ganz catheter or estimate LVEDP from other signs of myocardial failure.

When hypotension is present with high atrial pressures, positive inotropic drugs are needed. For rapid action, calcium chloride (100 to 200-mg doses, to a total of 2 to 3 gm) often is effective. A catecholamine by microdrip (isoproterenol, epinephrine, dopamine) provides smoother action for long-term support. Small doses of lanoxin often will increase contractility. In addition, the surgeon must finish his operation quickly, acidosis and hypoxemia must be abolished, and arrhythmias and rate problems treated with KCl, lidocaine, or atropine.

If the precarious circulation can be at least minimally maintained until anesthesia and the surgical procedure are ended, many of these high-risk patients will survive the postoperative period.

REFERENCES

1. Tarhan S, Moffitt EA, Taylor WF, et al: Myocardial infarction after general anesthesia. JAMA 220:1451-1454, 1972

2. White RD: Drugs in cardiac supportive care. Anesth Analg 55:633-639, 1976

Preanesthetic Evaluation and Management of Malignant Hyperthermia in the Pig Experimental Model

CHARLES E. SHORT, DVM, MS*
ROBERT R. PADDLEFORD, DVM†
CHARLES J. McGRATH, DVM‡
CHARLES H. WILLIAMS, PhD§
Columbia, Missouri‖

Fifty-three swine from the University of Missouri Sinclair Medical Research Farm were used in experimentation to determine their susceptibility to malignant hyperthermia, to determine appropriate anesthetic agents for susceptible swine and to investigate appropriate pharmaceutical agents which could protect against the development of malignant hyperthermia.

The screening technics used were successful in determining susceptible animals to MH and the anesthesia studies indicated that dissociative anesthetics had less tendency to trigger MH than did halothane and pancuronium was shown to have greater safety as a muscle relaxant than succinylcholine in this group of pigs. Pigs pretreated with reserpine had less tendency to develop symptoms of MH and some were completely protected. The principle undesirable effect was the development of hypotension if sufficient reserpine was used to provide total protection.

MALIGNANT hyperthermia (MH), a heritable disease which becomes of primary concern when a susceptible individual is exposed to anesthesia,[1] has caused widespread concern in man and is now being found with increasing alarm in swine.[2,3] MH has been reported in the dog[4] and cat,[5] and a suspected episode has occurred in the horse.[5a] The characteristics of the disease appear quite similar in animals[2-5] and in man,[6] and the hereditary predisposition is present in both, as is the higher incidence of the disease at younger age levels.[7,8]

Review of known cases of MH indicates that the development of symptoms may follow the administration of a large group of potent anesthetics and related agents, including halothane, methoxyflurane, ether, cyclopropane, succinylcholine chloride, d-tubocurarine chloride, gallamine, and multiple combinations of agents,[9] although it has been believed that local anesthesia, regional blocks, barbiturates, narcotics, neuroleptanalgesia, N_2O, and ketamine may be safely used in susceptible individuals.[8,10]

Individuals, animal or man, developing MH show an increase in body temperature (often progressing rapidly and uncontrollably), skeletal muscle rigidity, arrhythmias, hyperpnea, cyanosis, arterial O_2 desaturation, respiratory and metabolic acidosis, hyperphosphatemia, glucosemia, and, after initial hyperkalemia and hypercalcemia, possible hypokalemia and hypocalcemia.[11] As

*Professor, Department of Veterinary Medicine and Surgery, Department of Anesthesiology.
†Assistant Professor, Department of Veterinary Medicine and Surgery.
‡Resident, Department of Veterinary Medicine and Surgery.
§Assistant Professor of Medicine; Associate Professor of Biochemistry.
‖College of Veterinary Medicine, University of Missouri, Columbia, Missouri 65201.

Paper received: 3/17/75
Accepted for publication: 2/3/76

the condition progresses, there is an increase in serum levels of muscle enzymes. If the patient survives, muscle tenderness, weakness, and swelling are observed during the postanesthetic period. Serum creatine phosphokinase (CPK) levels are usually elevated before symptoms appear and increase further after the development of MH.[12] Serum aldolase, glutamic oxalic transaminase, hydroxybutyric dehydrogenase, and lactic dehydrogenase appear to be elevated after the disease.[13]

In man, preanesthetic histories and determination of CPK levels,[8] and when possible, muscle-tissue biopsies,[14] are of value in determining individual susceptibility.[15-17] In the experimental animal, an anesthetic challenge can be used as a screening test, with withdrawal of the agents immediately upon observation of symptoms. Determination of CPK values is probably the most widely used chemical test at present in man but is not absolute, since myocardial infarction, muscular disease, burns, and CO inhalation also can produce high levels of CPK.[18]

The etiology of MH is still debatable; studies have been made relative to the role of insufficient body adenosine triphosphate,[2,18] intracellular calcium metabolism,[2,19] uncoupling of oxidative phosphorylation, and reduction of muscle phosphorylase. The roles of single muscle cells versus muscle fiber responses and central action mediators versus peripheral have been studied,[6] as have the role of the sympathetic nervous system and of catecholamines before, during, or after the development of symptoms.[20]

The purpose of the present experiments was threefold:

1. To establish a protocol for more accurate screening of experimental animals.

2. To supply additional information for the safe selection of agents to be used for anesthesia where susceptibility to MH is known or suspected.

3. To test the hypothesis that MH relates to neurohumoral transmission of the adrenergic nervous system.

MATERIALS AND METHODS

Fifty-three swine were divided into 4 groups according to the phase of the research to be completed. Group I consisted of 34 pigs of similar age and size, averaging ± 9 kg each at the beginning of the study, and all with known hereditary probability for MH susceptibility.

Group II consisted of 10 pigs in the 7.5 to 10-week-old age range, averaging ± 9 kg each. These pigs were the offspring of MH-susceptible parents.

Group III (3 pigs, ± 46 kg each) served as controls, since there was no history of MH in their breeding stock.

Group IV (6 pigs) were unsusceptible subjects, used to ascertain whether the anesthetic technics and agents employed in this study could cause MH in unsusceptible subjects.

Halothane was administered by one of 3 standard anesthetic units: a Foregger Foretrend® 100; a North American Drager; or a Foregger Eiffel® model. When N_2O was used in conjunction with halothane, it was usually given at the ratio of 1:1 v/v with O_2. N_2O flows never exceeded 80 percent of total volume when used as the primary agent. O_2 flow rates were never allowed to drop below 1 L/min, usually ranging from 2 to 4 L/min. Whenever there was respiratory depression or arrest, adequate ventilation was provided by immediate manual or mechanical respiration, usually with a bird® Mark 7 respirator operated at 30 cm of H_2O, unless otherwise specified.

Cardiac electrophysiology was monitored by a Tektronix® model 410 oscilloscopic ECG monitor, and blood pressure by an indirect ultrasonic monitor. An Instrumentation Laboratories micro-blood-gas analysis system was used for blood gases and pH measurement; and for more detailed physiologic studies, a Hewlett-Packard multichannel oscilloscopic monitor with hot stylus printout for recording data.

Agents used, in addition to halothane, N_2O, and O_2, included sodium thiamylal, for ultrashort barbiturate inductions; ketamine, or a tiletamine-zolazepam combination,* for dissociative anesthesia; Innovar® for neuroleptanalgesia; succinylcholine or pancuronium for muscle relaxation; and methyldopa or reserpine for autonomic nervous system effects.

Methodology.—The method of identifying pigs susceptible to the MH syndrome was as follows:

*Tiletamine-zolazepam: CI-744, anesthetic under development, Parke, Davis & Company, Ann Arbor, Michigan.

Halothane (4%) in 2 L/min O_2 was administered for 60 seconds, after which the concentration was reduced to 2 percent. After the development of relaxation and the induction of anesthesia, halothane levels were adjusted for the maintenance of a surgical plane of anesthesia. While this initial concentration exceeds normal MAC values for induction, it was important in these experiments to create the availability of a high concentration of halothane to initiate responses indicative of MH, if possible. Animals were considered "susceptible" to MH when 2/3 of the following characteristics were seen with halothane within 20 minutes, and considered "normal" if such response did not follow:

a. A heart rate exceeding 200 bpm.

b. An increase in rectal temperature of 1° F.

c. Development of muscle rigor.

Normal in this context does not imply that the animals would not be susceptible to the development of MH with a similar challenge at a later date or to a challenge from another product.

Since one of our objectives was to find additional ways to anesthetize swine and reduce the risk of MH, ketamine was administered at the rate of 11 mg/kg body weight. Since ketamine leaves some muscle resistance in the pig, the tiletamine-zolazepam combination was administered at the rate of 6.6 mg/kg body weight, for comparison.

As part of the experimentation, effects of those methods of administering anesthesia which had tended to develop symptoms of MH in man were studied in these animals, to learn if similar responses could be expected. This included induction and maintenance by barbiturates, induction by Innovar, maintenance by N_2O-O_2, by halothane, and the use of succinylcholine (1.1 mg/kg) for muscle relaxation. Since succinylcholine and pancuronium have both been incriminated in producing MH in humans, these were also used as test agents. Pancuronium was administered at 2 levels in a 2-part trial, giving 0.11 mg/kg IV in the 1st portion and 0.22 mg/kg IV in the second.

Prophylaxis.—Studies included administration of methyldopa or reserpine to susceptible individuals, to determine whether these might prevent the developmnt of MH. There has been considerable attention to the effect of the monamine oxidase inhibitors and to the role of beta-adrenergic blockers, and whether these effects are created relative to central or to peripherally acting causes. To test the hypothesis that MH could be an autonomic nervous system response, 5 animals were given 5 mg of methyldopa twice daily. After 3 days, they were exposed to halothane anesthesia, using methods similar to those described.

Ten pigs of group II were similarly tested with reserpine. In the 1st trial, using reserpine only, 1 animal was given 0.22 mg/kg, administered for 2 days prior to challenge with halothane anesthesia. Five other reserpine-treated pigs, weighing from 20.8 to 34 kg, were given 0.5 mg/pig IM, 24 hours before halothane challenge, to determine a more specific effective dosage range. An additional 9 pigs each received 0.0275 mg/kg IM daily for 2 treatments prior to halothane. The last reserpine experiment was divided into 3 components, consisting of group A, 3 pigs given 0.045 mg/kg for 2 days prior to anesthesia; group B, 3 pigs given the same dose but for 3 days; and group C, 2 pigs receiving 0.045 mg/kg of reserpine IM for 4 days prior to anesthesia.

Supported in part by the Department of Medicine, University of Missouri College of Medicine and the Department of Veterinary Medicine and Surgery, College of Veterinary Medicine.

RESULTS AND DISCUSSION

Susceptibility Studies.—Even though it has been reported that MH has hereditary linkage, and although the animals used in this study were the offspring of known carriers of this hereditary potential, it was essential to experimental design that each animal be subjected to anesthetic challenge to determine the extent of its MH susceptibility (table 1).

The anesthesia record (fig 1) exemplifies a susceptible animal receiving an ultrashort barbiturate (thiamylal) induction with a preanesthetic administration of atropine and maintained on N_2O and O_2 for 1.5 hours before administration of halothane. It was maintained at a satisfactory plane of anesthesia and did not develop any symptoms of MH until after the initiation of halothane anesthesia.

These animals maintained adequate blood pressure and cardiovascular responses and showed little evidence of cardiac dysrhythmias. Their blood pH and blood-gas values

TABLE 1

Responses of Swine to Halothane Challenge for Determination of MH Susceptibility

	Heart rate at onset of rigor	Respiratory rate at onset of rigor
Group I, 34 pigs		
29 reactors to halothane*	227 ± 40 beats/min	59 ± 22 breaths/min
5 reactors to halothane (in later test, positive to succinylcholine challenge)	151 ± 16 beats/min	29 ± 7 breaths/min
Survival rate: 100%		
Reaction time: 2-16 min		
Group II, 10 pigs		
10 reactors to halothane*	212 ± 33 beats/min	29 ± 6 breaths/min
Survival rate: 100%		
Reaction time: 113 ± 60 sec		
Group III, 3 pigs		
3 reactors—halothane continued 5 min after beginning of rigor		
Survival rate: 0%		
Time from start of response until death: average 27 min		

*Halothane started via mask at 4% concentration for 60 sec, then reducing to 2% and then to maintenance of surgical plane anesthesia. Anesthesia stopped for groups I and II when rigor started.

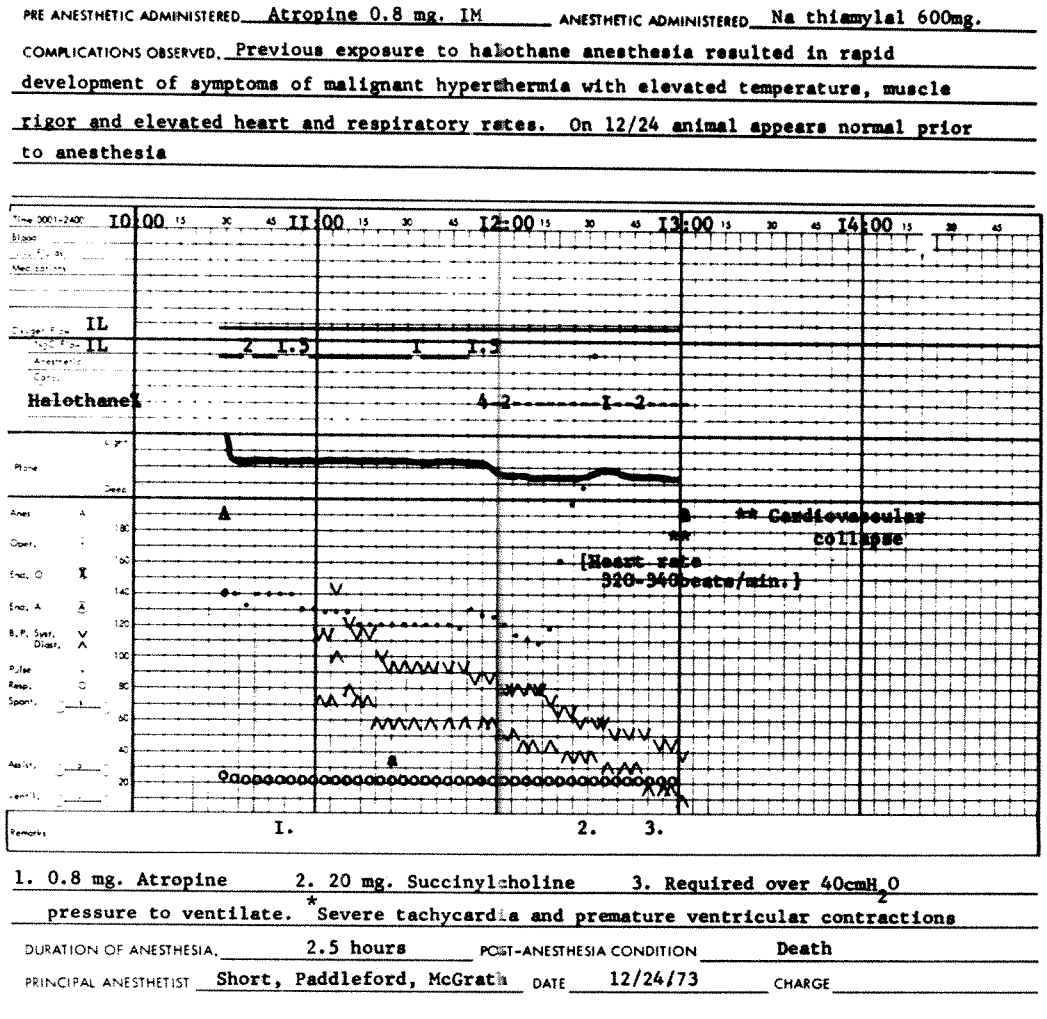


FIG 1. Anesthesia record for pig showing typical symptoms of malignant hyperthermia.

were within normal limits, with the exception of an elevated CO_2. This was compensated by added ventilation. After the initiation of halothane anesthesia, there was a drop in blood pressure, associated premature ventricular contractions, and these problems were exaggerated further after the administration of succinylcholine.

At this time, heart rate increased drastically, producing a severe tachycardia with inadequate blood pressure and difficulty in maintaining positive-pressure breathing, due to intracostal muscle rigidity. Even with halothane anesthesia in the presence of succinylcholine, there was extreme muscle rigidity, and after 2.5 hours of anesthetic management, the animal succumbed to cardiopulmonary collapse. This example of the typical responses seen in the experimental pig susceptible to MH when subjected to anesthetic management demonstrates the similarities to human patient responses.

Another pig (fig 2) demonstrated that the use of Innovar as an inducing agent to be followed by N_2O-O_2 does not always prevent MH symptoms in susceptible animals. This is somewhat in contrast to the concept that, for individuals susceptible to MH, narcotic or neuroleptanalgesia administration may be considered safe.

Use of Pancuronium.—After it was determined that susceptible animals might be expected to react to the administration of succinylcholine with a high degree of regularity, the possibilities of the administration of pancuronium as a muscle relaxant that might have some protective qualities were evaluated. In the animal (fig 3) to which 1.6 mg (0.22 mg/kg) of pancuronium was administered on 2 occasions, followed by 20 mg (2.1 mg/kg) of succinylcholine IV, no MH symptoms developed, in contrast to cases where succinylcholine was administered without pancuronium. This was later to be of significance, since it indicated the potential use of pancuronium as a muscle

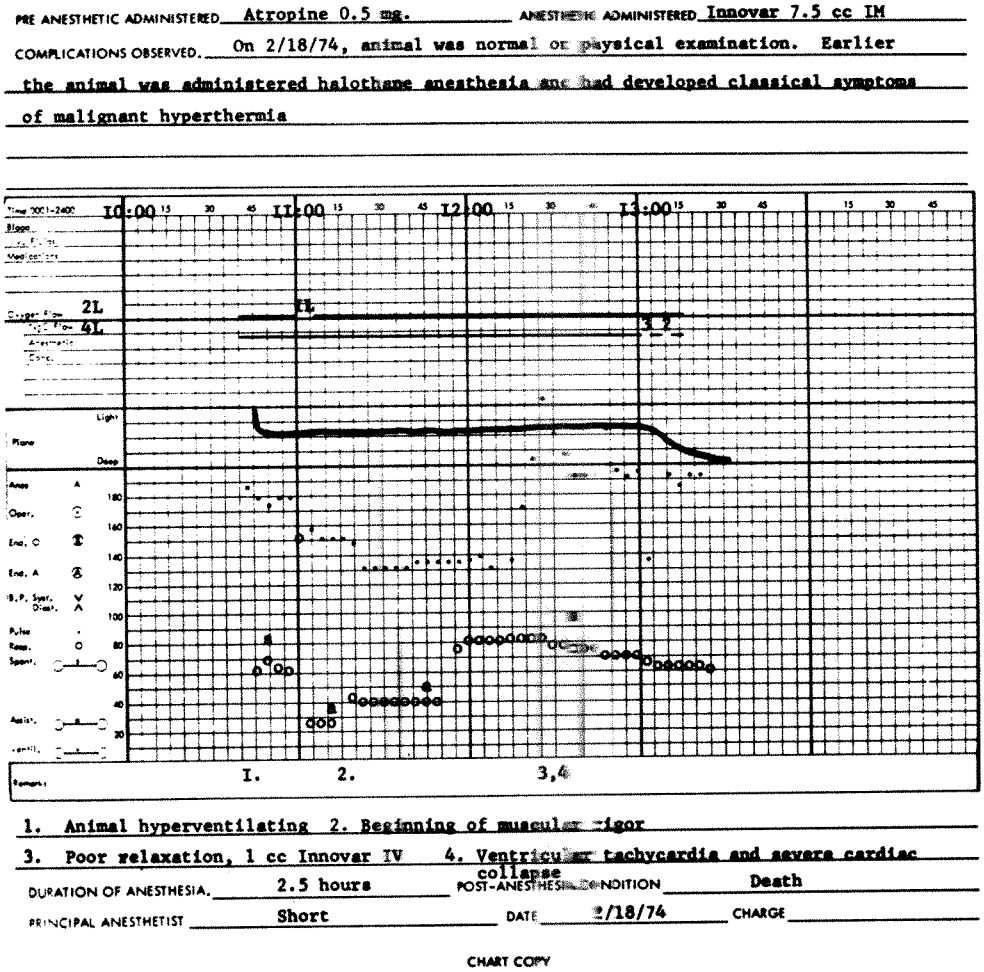


FIG 2. Anesthesia record for pig developing malignant hyperthermia with Innovar and N_2O.

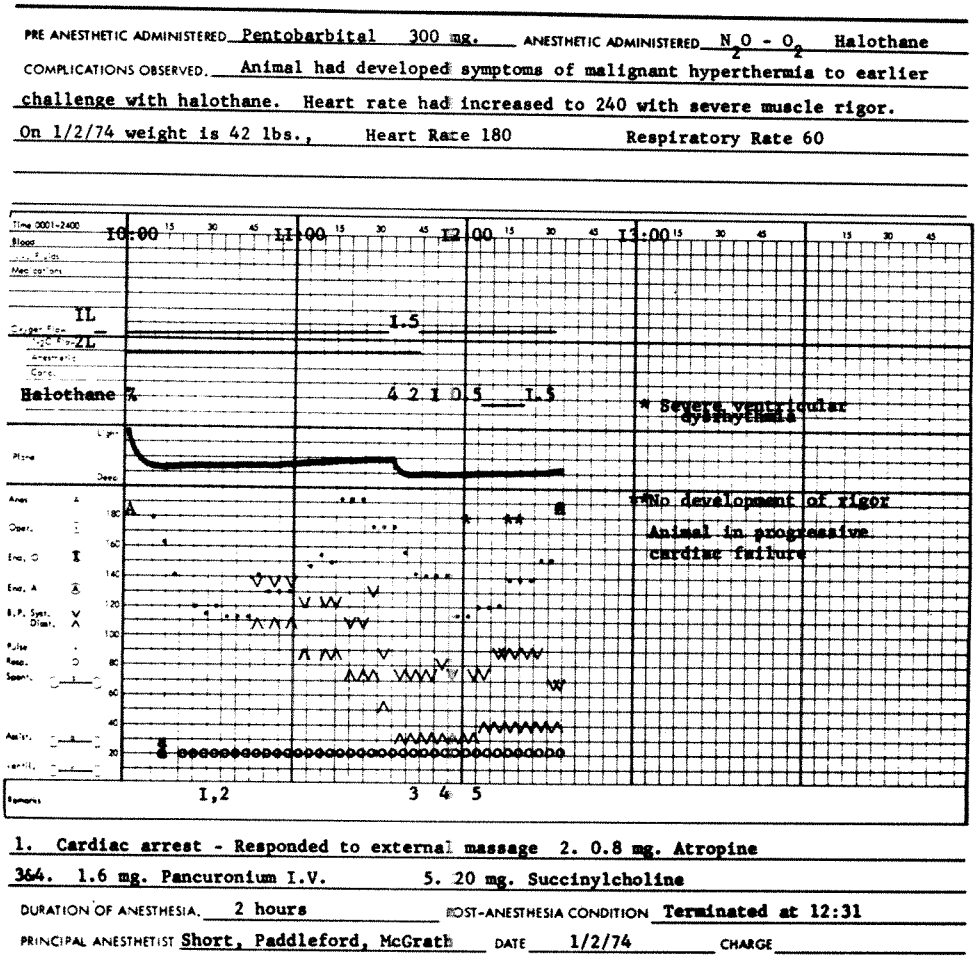


FIG 3. Anesthesia record illustrating lack of development of malignant hyperthermia to succinylcholine following pancuronium.

relaxant in animals susceptible to MH. Heart rates remained stable and adequate in all animals (table 2) and cardiac dysrhythmias did not appear. Respiration was maintained with a bird® mechanical ventilator and a 30 cm H_2O pressure/breath and maintaining the animals at 16 to 29 breaths/min.

Blood pressure in pancuronium-treated animals remained stable, although somewhat elevated, in pigs given the smaller dose. Relaxation followed in each individual pig within 1 minute after injection, lasting 6.5 minutes after the low dose and 14 minutes after the higher dose. Body temperature did not significantly change from pretreatment values.

Injectable Anesthetics (table 3).—Induction time was 3 minutes for both ketamine and tiletamine-zolazepam, and duration of anesthesia was 10.5 minutes for ketamine and 14 minutes for tiletamine-zolazepam. Heart rates remained stable for ketamine; with tiletamine-zolazepam, there was a drop in heart rate but it stabilized at an adequate level after 5 minutes. Respiratory rates were elevated with ketamine but remained at normal levels with the drug combination. It was not possible to accurately record blood pressures in the ketamine-treated pigs because of slight muscle tremors, but stable blood-pressure levels were observed in all animals anesthetized with the combination. Body temperatures remained stable with the ketamine-anesthetized pigs in spite of muscle tremors, and body temperature dropped during the maintenance of anesthesia with tiletamine-zolazepam.

Failure to develop MH symptoms with ketamine in spite of the degree of muscle activity during the anesthetic period is of

TABLE 2

Responses of MH-Susceptible Swine to Pancuronium

Time, min	0	5	10	15
			Heart rate, beats/min	
A*	191 ± 24	179 ± 27	157 ± 28	—
B†	202 ± 25	189 ± 24	182 ± 16	175 ± 28
A	29 ± 10		Respiratory rate, breaths/min	
B	16 ± 0		Rate and volume controlled by mechanical ventilation 30 cm H_2O pressure	
			Blood pressure, torr	
A	140 ± 36 / 84 ± 49			
B	186 ± 13 / 129 ± 26	185 ± 10 / 124 ± 12	161 ± 18 / 112 ± 25	
			Time from injection to paralysis	
A	1 min			
B	1 min			
			Time from paralysis to recovery	
A	6.5 ± 3 min			
B	14 ± 3 min			
	Pretreatment temperature, °F		Post-treatment temperature, °F	
A	102.5 ± 0.5		102.4 ± 0.6	
B	102.2 ± 0.8		102.2 ± 0.6	
A	0.11 mg/kg pancuronium IV			
B	0.22 mg/kg pancuronium IV			
	No other medication used concurrently			

*Six pigs in group A.
†Four pigs in group B.

TABLE 3

Responses of MH-Susceptible Swine to Ketamine and a Related Anesthetic

Time, min	0	5	10	15
			Heart rate, beats/min	
A*	149 ± 22	138 ± 18	133 ± 17	—
B†	176 ± 49	131 ± 20	127 ± 18	127 ± 21
			Respiratory rate, breaths/min	
A	93 ± 22	93 ± 19	91 ± 26	—
B	46 ± 25	55 ± 6	67 ± 7	67 ± 10
			Blood pressure, torr	
A	Unable to record due to tremors			
B	144 ± 35 / 83 ± 25	150 ± 31 / 82 ± 27	152 ± 36 / 81 ± 26	135 ± 8 / 68 ± 26
	Induction times		Surgical anesthesia duration	
A	3 min		10.5 ± 1.9 min	
B	3 min		14.0 ± 3.0 min	
	Preanesthetic temperature, °F		Postanesthetic temperature, °F	
A	102.5 ± 0.6		102.5 ± 0.6	
B	102.4 ± 0.5		101.4 ± 0.5	
A	Ketamine HCl—11 mg/kg IM			
B	Tiletamine-zolazepam—6.6 mg/kg IM			

*Four pigs in group A.
†Five pigs in group B.

interest, since it was postulated that one of the reasons for the development of MH after succinylcholine administration is the severity of muscle rigidity and fasciculations shortly after administration. However, the degree of muscular activity after ketamine was mild compared with fasciculations after succinylcholine administration; perhaps herein lies the difference in effect.

Methyldopa and Reserpine Tests.—An initial trial of methyldopa in 5 animals known to be susceptible to MH showed a marked degree of protection against the development of MH symptoms from halothane exposure. However, although methyldopa blocks the synthesis of the mediator of adrenergic transmission, thus providing protection against development of MH, severe hypotension was an undesirable side effect.

As a result, the next step of the study involved chemical transmission and storage of a mediator; for this, the drug selected was reserpine (fig 4). In the animal whose chart is shown, body temperature dropped below control values during anesthesia. The animal was hypotensive, and even though it showed no MH symptoms and made an uneventful recovery after 45 minutes of anesthesia, the outcome was progressive cardiovascular collapse ending in death 3 days after the trial. Because of this undesirable result, a subsequent trial used 5 pigs, varying in weight from 20.8 to 34 kg, and given a single dose of 0.5 mg/pig IM 24 hours before halothane challenge. In these pigs, protection increased from 1.9 ± 1 minute to 6.4 ± 4 minutes after the administration of the reserpine (table 4). Protection was dose

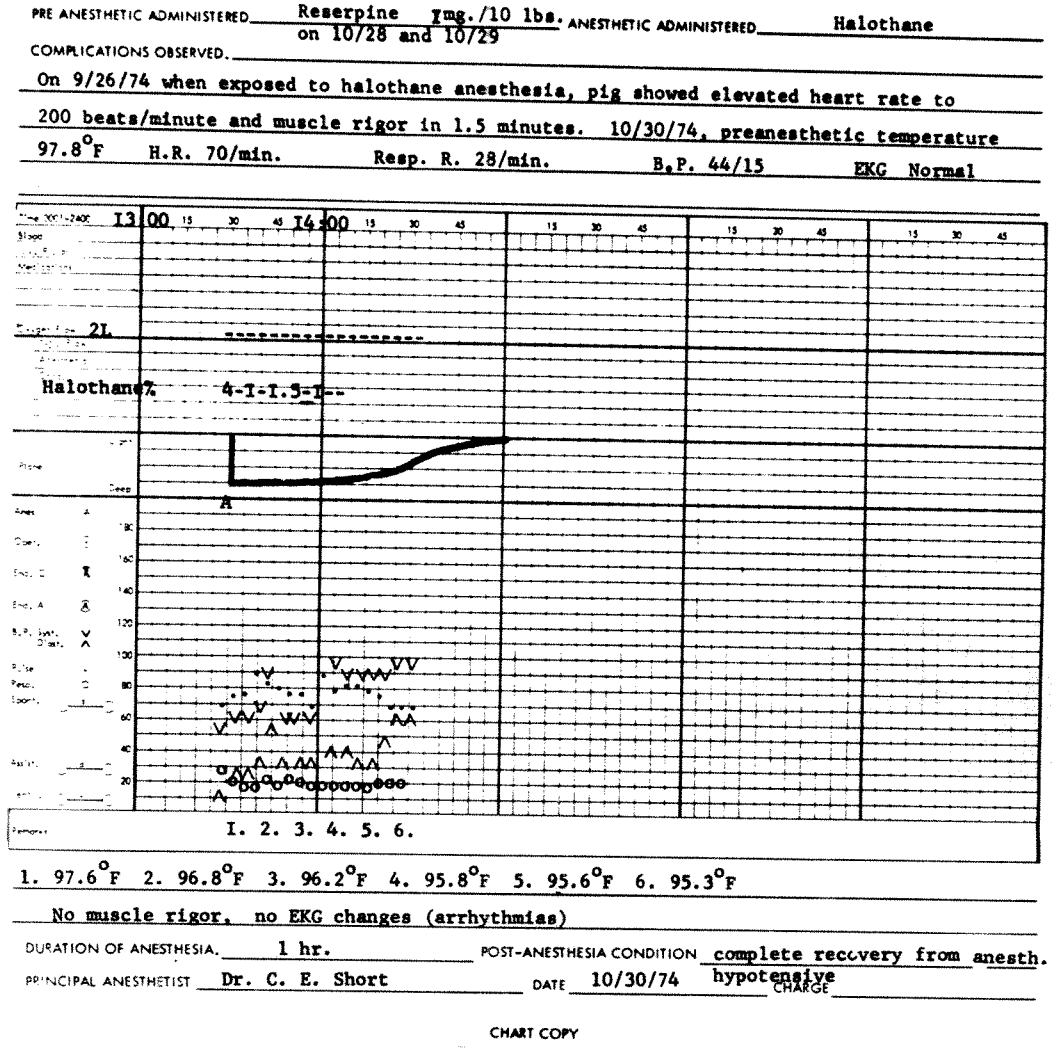


FIG 4. Anesthesia record of pig protected against malignant hyperthermia by reserpine.

TABLE 4
Reserpine Tolerance and Efficacy Trial Results* in 5 Animals

Time:	Beginning of halothane administration	5 minutes later
	Heart rate 201 ± 11	Heart rate 20 ± 23
	Respiratory rate 31 ± 4	Respiratory rate 31 ± 3
	Blood pressure $\frac{97 \pm 17}{40 \pm 15}$	
	Time of reaction 6.4 ± 4 min	
	Time of reaction of same animals without reserpine 1.9 ± 1 min	
	Survival 100%	

*Dosage: 0.5 mg total dose/pig IM 24 hours before halothane challenge.
Weights ranged from 20.8 to 34 kg.

TABLE 5
Reserpine Tolerance and Efficacy Trial*

Time:	Beginning of halothane	10 min	20	30	35	40	45
				Heart rate, beats/min			
	173 ± 21	160 ± 27	124 ± 30	136 ± 27	—	123 ± 22	—
				Respiratory rate, beats/min			
	30 ± 10	24 ± 9	24 ± 14	24/30 cm H_2O pressure via mechanical ventilation			
				Blood pressure, torr (means)			
	$\frac{96}{24}$	$\frac{77}{20}$	$\frac{72}{20}$	$\frac{66}{20}$	$\frac{72}{25}$	$\frac{62}{25}$	$\frac{81}{40}$
				Body temperature, °F			
	101.5 ± 1.3	101.2 ± 1.2	101.4 ± 1.1	101.4 ± 1.1	—	—	101.2 ± 1

Reactions

2 reacted to halothane within 2 min.

1 reacted to halothane within 15 min.

6 were protected throughout halothane challenge of 30-min duration.

4 were protected to succinylcholine challenge.

1 was not protected to succinylcholine and died with MH.

*Dosage: 0.0275 mg/kg IM daily for 2 treatments prior to halothane in 9 animals. 1.1 mg/kg succinylcholine administered IV in 5 animals. Five of these were given succinylcholine.

related in linear fashion. All animals survived.

With reserpine (0.0275 mg/kg) given IM for 2 daily treatments before halothane anesthesia (table 5), 2/9 pigs reacted to halothane administration within 2 minutes and a third reacted with muscle rigor after 15 minutes. Halothane challenge in 3 pigs was discontinued immediately upon the development of muscle rigidity, and all survived. Six pigs were protected throughout the halothane challenge of 30-minute duration. Five of the 6 protected to halothane challenge were subsequently challenged with succinylcholine at 1.1 mg/kg. Four of the five did not show the typical symptoms of MH. Body temperatures were maintained at acceptable levels throughout the procedure in the 4 protected animals, and cardiopulmonary responses were within normal limits with the exception of blood pressure, which dropped at times to levels unacceptable for safe anesthetic management.

TABLE 6

Reserpine Tolerance and Efficacy Trial in 8 Animals*

Time, min	0	5	10	15	20
			Heart rate		
A	195 ± 13	173 ± 12			
B	125 ± 13	127 ± 6	123 ± 13	127 ± 21	135 ± 23
C	125 ± 7	118 ± 4	120 ± 1	118 ± 4	112 ± 3
			Respiratory rate		
A	22 ± 2.8				
B	15 ± 8	17 ± 6	23 ± 10	25 ± 5	18 ± 8
C	28 ± 11	12 (placed on ventilator)			
			Blood pressure, torr		
A	107 ± 3 / 27 ± 12				
B	107 ± 3 / 25 ± 9	79 ± 22 / 23 ± 6	68 ± 29 / 30	58 ± 28 / 21	65 ± 17 / 22
C	92 ± 14 / 30 ± 14	75 ± 10 / 22	69 / 20	60 / 20	54 / 20
			Temperatures, °F		
A	102.6 ± 0.6				
B	102.0 ± 9	102.0 ± 1.2	102.1 ± 1.9	102.3 ± 2	102.2 ± 1.6
C	102.2	102.2	101.8	102.9	103
			Time of rigor		
A	3 min				
B	18 ± 6 min				
C	Did not occur within 30 min				
			Results		
A	Halothane discontinued—100% survival				
B	Halothane discontinued—66% survival				
C	100% survival to MH, 50% to cardiovascular collapse				

*Dosage: A. 0.045 mg/kg per day for 2 days.
B. 0.045 mg/kg per day for 3 days.
C. 0.045 mg/kg per day for 4 days.

Since complete protection was not obtained at the 0.0275 mg/kg drug level, reserpine was given to 4 pigs at 0.045 mg/kg for 2 days, in a 2nd trial for 3 days, and in a 3rd trial for 4 days (table 6). Heart rates were elevated in group A and there was no marked degree of hypotension. These animals, however, reacted to halothane challenge with the development of rigor within 3 minutes. Pigs in group B had a slower heart rate and normal respiratory rate. Blood pressure was depressed, with a noticeable degree of hypotension. Rigor did not develop from the halothane challenge until 18 minutes after the onset of anesthesia. All these animals survived after the discontinuance of anesthesia with the exception of 1 animal whose temperature continued to rise, with other symptoms of MH. It died 2 hours later with a temperature of 111.9° F.

In group C, normal heart and respiratory rates were found, with a marked degree of hypotension; body temperatures were normal; none of the animals in this trial reacted to over 30 minutes of halothane anesthesia; and all survived to the challenge for development of MH. However, half of the animals died later with cardiovascular collapse from the reserpine.

CONCLUSIONS

Our method of challenge for the determination of MH-susceptible animals studied relative to the MH syndrome is effective and reproducible.

Six animals given succinylcholine developed MH, while animals given only pancuronium did not develop MH at either of 2 dosage levels, nor did the animals receiving succinylcholine after they were relaxed with pancuronium. Thus pancuronium may be a safer muscle relaxant than succinylcholine for use in MH-susceptible animals. Since animals treated with methyldopa did

not develop MH, as they had under control conditions, there is evidence that blocking of the transmission of adrenergic mediators, for example norepinephrine, lends itself to provide protection of susceptible animals to agents known to produce MH.

Reserpine studies indicate that this drug can be as effective as methyldopa in protecting susceptible animals and is more controllable, as methyldopa dosage levels which will afford protection against MH development also cause severe hypotension.

REFERENCES

1. Thompson MW: Some principles of medical genetics, International Symposium on Malignant Hyperthermia. Springfield, Illinois, Charles C Thomas, Publisher, 1973, pp 59-66

2. Jones EW, Kerr DD, Nelson TE: Malignant hyperthermia observations in Poland China pigs, International Symposium on Malignant Hyperthermia. Springfield, Illinois, Charles C Thomas, Publisher, 1973, pp 331-338

3. Nelson TE, Jones EW, Bedell DM: Porcine malignant hyperthermia: a study on the triggering effects of succinylcholine. Anesth Analg 52:908-911, 1973

4. Short CE, Paddleford RR: Malignant hyperthermia in the dog. Anesthesiology 39:462-463, 1973

5. deJong RH, Heavner JE, Amory DW: Malignant hyperpyrexia in the cat. Anesthesiology 41:608-609, 1974

5a. Klein LV: Case report—a hot horse. Vet Anesthesia 2:41-42, 1975

6. Britt BA, Kalow W: Malignant hyperthermia. Aetiology unknown. Can Anaesth Soc J 17:316-330, 1970

7. Kalow W, Britt BA: Inheritance of malignant hyperthermia, International Symposium on Malignant Hyperthermia, Springfield, Illinois, Charles C Thomas, Publisher, 1973, pp 67-76

8. King JO, Denborough MA: Anesthetic induced malignant hyperpyrexia in children. J Pediat 83:37-40, 1973

9. Britt BA, Kalow W: Malignant hyperthermia. A statistical review. Can Anaesth Soc J 17:293-315, 1970

10. Brown LL, Britt BA: Malignant hyperthermia. South Med J 67:799-804, 1974

11. Britt BA: Recent advances in malignant hyperthermia. Anesth Analg 51:841-850, 1972

12. Isaacs H: High serum creatine phosphokinase levels in asymptomatic members of the families of patients developing malignant hyperpyrexia, International Symposium on Malignant Hyperthermia. Springfield, Illinois, Charles C Thomas, Publisher, 1973, pp 311-338

13. Britt BA: Prevention of malignant hyperthermia, International Symposium on Malignant Hyperthermia, Springfield, Illinois, Charles C Thomas, Publisher, 1973, pp 451-461

14. Mills DE, Marcy JH: Case history number 65: Malignant hyperthermia with subsequent uneventful general anesthesia. Anesth Analg 50:1104-1112, 1971

15. Ellis FR, Harriman GF: A new screening test for susceptibility to malignant hyperpyrexia. Br J Anaesth 45:638, 1973

16. Imes RKR, Stromme JH: Rise in serum creatine phosphokinase associated with agents used in anaesthesia. Br J Anaesth 45:185-190, 1973

17. Mounds RF, Denborough MA: Identification of susceptibility to malignant hyperpyrexia. Br Med J 2:245-247, 1974

18. Anido V, Conn RB, Mengoli HF, et al: Diagnostic efficacy of myocardial creatine phosphokinase using polyacrylamide disk gel electrophoresis. Am J Clin Pathol 61:599-605, 1974

19. Harrison GG: Recent advances in the understanding of anaesthetic induced malignant hyperpyrexia. Anaesthesist 22:373-376, 1973

20. Summers RJ: Interaction between monomine oxidase inhibitors and anesthetics, International Symposium on Malignant Hyperthermia. Springfield, Illinois, Charles C Thomas, Publisher, 1973, pp 363-379

Sodium Nitroprusside-Induced Hypotension for Supine Total Hip Replacement

NOEL W. LAWSON, MD*
DOLA S. THOMPSON, MD†
CARL L. NELSON, MD‡
JOAN W. FLACKE, MD§
EDWARD R. NORTH, MD‖
Little Rock, Arkansas**

Deliberate hypotension was produced during general anesthesia by the infusion of sodium nitroprusside in 13 patients undergoing total hip replacement. Hemodynamic data from these patients were compared with those obtained from 5 patients under normotensive anesthesia for the same procedure. During the hypotensive period, which averaged 1.5 hours, the cardiac index rose 20 percent compared with controls. No acidotic tendency was seen. Blood loss in the study group averaged 475 ml, compared with 1475 ml in controls. From these data, a dose-response curve was derived which may allow the accurate prediction of the minute dosage of sodium nitroprusside required to safely induce hypotension during anesthesia.

TECHNICS to recover or reduce blood loss during surgical procedures in current use include deliberate hypotension during anesthesia, hemodilution, and several variations of autologous blood transfusion. Deliberate hypotension during anesthesia to reduce intraoperative blood loss was first used over 25 years ago.[1] Although introduced during an era when the risk of homologous blood transfusion was prodigious, this concept was controversial. As transfusion became safer during the 1950s, the popularity of hypotensive anesthesia waned. The risks of transfusion could no longer be equated with those of deliberate hypotension; nevertheless, in a 1969 report,[2] more than 5 percent of all patients receiving blood transfusions showed unfavorable reaction.

Today, induced hypotension is enjoying a revival, not only as a means to reduce the risks of and need for transfusion but also as a means of conserving a scarce national resource. Of the technics used to produce deliberate hypotension during anesthesia, none have proven ideal.[1] Of these, sodium nitroprusside, a potent but evanescent antihypertensive drug, has been used in some centers since 1962.[3] Scant data are available, but nitroprusside, in contrast to other technics, reportedly enhances cardio-circulatory dynamics,[4-7] producing arteriolar vasodilation independent of the autonomic nervous system. It was first used by Johnson[8] in 1929 for the treatment of hypertensive crisis and only recently became available commercially in the United States.

*Associate Professor, Department of Anesthesiology.
†Professor, Department of Anesthesiology.
‡Professor, Department of Orthopedics.
§Assistant Professor, Department of Anesthesiology.
‖Chief Resident, Department of Orthopedics.
**University of Arkansas School of Medicine, Little Rock, Arkansas 72201.

Paper received: 11/24/75
Accepted for publication: 2/2/76

Several reports indicate that the inherent properties of nitroprusside are useful in a variety of unrelated clinical situations. Specifically, cardiologists[9] report improved cardiac output and tissue perfusion with the infusion of nitroprusside in patients with failing hearts and cardiogenic shock—a situation analogous to the myocardial depression produced by general anesthesia. This paper reports the results of a study in which cardiac output and other physiologic parameters were measured in 13 selected patients during halothane-N_2O-O_2 anesthesia and sodium nitroprusside-induced hypotension for total hip replacement.

METHODS

Thirteen patients of the Jehovah's Witness faith, ranging in age from 9 to 78 years, made up the study population. Patients with cerebrovascular disease, clinical or electrocardiographic evidence of ischemic heart disease, renal hypertension, serious peripheral vascular disease, or severe obstructive lung disease were excluded from the study. Extreme age was not considered a contraindication. Various hemodynamic measurements from this group were compared with data obtained from 5 patients, also undergoing total hip replacement, using the same but normotensive anesthesia.

Premedication consisted of morphine, diazepam, and scopolamine, except in patients over age 60, in whom the morphine was omitted. Anesthesia was induced in both groups with 2 percent thiamylal IV and maintained with halothane-N_2O-O_2 (50:50). Stable surgical anesthesia was maintained in all cases with an inspired halothane concentration of between 0.5 to 0.75 percent. Succinylcholine was used to facilitate endotracheal intubation. Five percent dextrose in lactated Ringer's solution was administered to both study groups at a rate of 12 to 15 ml/kg body weight the 1st hour and 6 to 10 ml/kg/hr thereafter. Homologous blood was not given to the control patients unless more than 500 ml of blood loss was anticipated. Positive-pressure ventilation was not used as a deliberate aid in producing hypotension; however, ventilation was assisted as needed to produce a $Paco_2$ between 37 and 41 torr. Nondepolarizing muscle relaxants were purposely omitted to avoid additional hemodynamic effects. In both study and control groups, the operation was performed with the patient supine, with slight hip elevation.

Arterial hypotension was induced in the study group by the continuous infusion of a 0.01 percent solution (100 μg/ml) of sodium nitroprusside in 5 percent dextrose in water just before the skin incision. The drug was delivered by a constant-infusion pump,* allowing accurate control of the dosage. The initial dose was 100 μg/min; this was adjusted later in order to produce the desired degree of hypotension, which was determined by bleeding from the operative site rather than by an arbitrary level of blood pressure. Infusion of nitroprusside was discontinued, and blood pressure allowed to return to normal before wound closure so that hemostasis could be assessed.

Arterial blood pressure, pulse rate, ECG, central venous pressure (CVP), urine output, and tympanic temperature were monitored continuously. The arterial blood pressure was monitored electronically through a cannula inserted percutaneously into the radial artery before the induction of anesthesia. A CVP cannula was inserted also at this time through a convenient vein. Its position was ascertained clinically by advancing the catheter within the thorax until oscillation in manometric pressure was noted with the respiratory cycle and heart beat. Proper positioning was confirmed postoperatively by x-ray. An indwelling urinary catheter was inserted after induction of anesthesia into all patients of both study groups. The ECG (lead II) was monitored by oscilloscope.

Cardiac output and arterial blood gases were measured 6 times during the perioperative period. In both study and control patients, measurements were made before induction of anesthesia and after 30 minutes of stable normotensive anesthesia. In the hypotensive study group, cardiac output was measured again 20 minutes after achieving stable hypotension and 3 minutes after acrylic cement was inserted into the femoral shaft. In the normotensive group, the measurements were made at corresponding times.

Finally, cardiac output was determined in both groups in the normotensive stage during wound closure and in the recovery room. Indocyanine green was injected rapidly into the CVP cannula and blood was withdrawn at a constant rate from the radial artery through a densitometer connected to a Lexington Instruments Model COC-SD cardiac output computer system. Dye curves and

*Harvard Apparatus Company, Millis, Massachusetts.

the computer analog output were recorded simultaneously on the previously calibrated dual-channel Linear Instruments chart recorder. Duplicate cardiac output was measured at each study interval and the data accepted when sequential determinations differed by less than 0.3 L/min. Total peripheral resistance (TPR), cardiac index (CI), and stroke volume (SV) were calculated from the above data.*

Blood loss was estimated by the amount in suction bottles and by weighing sponges. Irrigation fluid was collected by a separate suction system.

RESULTS

Hemodynamics.—The anesthetic management and hemodynamics of both study and control patients were essentially the same up to the point when hypotension was induced in the study group. The mean combined preinduction CI for both groups was above normal (4.25 L/min/m) with a wide spread of values ranging from a normal of 3.0 L/min/m to a high of 5.5 L/min/m. This elevation and spread of values was expected and thought to reflect various degrees of preoperative anxiety.

The statistical mean of the mean preinduction arterial blood pressure was 112 ± 5 torr. Following induction and after 30 minutes of stable, normotensive anesthesia, the mean CI of both groups fell to 2.32 L/min/m, representing a much narrower range of values. The decrease in CI was statistically significant ($p<0.01$, paired t-test). During this transition from awake to asleep, there was a moderate reduction in heart rate and the blood pressure returned to a normal mean value of 98 torr in both groups.† No significant CVP change was noted.

Hypotension was induced in the 13 study patients with nitroprusside and the dosage adjusted to obtain a blood pressure compatible with a dry surgical field. The statistical MAP achieving this condition was 64 ± 4 torr,† a 43 percent decrease from a mean preinduction blood pressure of 112 torr. The CI, measured after 20 minutes of stable hypotension, rose 20 percent from normotensive levels to a nearly normal CI of 2.95 L/min/m (fig 1). This parameter remained stable throughout the hypotensive period. However, the CI returned to the lower prehypotensive level when the nitroprusside infusion was discontinued. The difference in mean increase in CI during hypotension was statistically significant compared with that of normotensive controls, which remained depressed throughout the procedure ($p<0.01$, paired t-test) (fig 2).

Compensatory alterations in heart rate and CVP during induced hypotension were unpredictable. The heart rate either remained the same or rose slightly upon initiation of hypotension. Similarly, there was either no change or a slight fall in CVP. In those instances (3 patients) where heart rate rose and CVP fell, infusion of additional fluid restored these values toward normal without affecting the level of hypotension.

The mean calculated SV during normotensive anesthesia was 59 ± 7 ml for both study and control patients, increasing to a mean of 71 ± 5 ml during nitroprusside infusion, whereas no significant change was noted in the control patients. This 17 percent rise in SV during nitroprusside hypotension paralleled but did not match the rise in CI. These data were influenced by the 3 patients who developed an increase in heart rate and a fall in CVP at the initiation of deliberate hypotension. However, SV increased in these patients when the CVP and heart rate returned to normal with the infusion of fluid. The increase was noted when the 2nd set of cardiac output determinations were made following the insertion of the acrylic cement into the femoral shaft.

The mean preinduction TPR for both groups was 1373 dynes/sec/cm^{-5}. Mean TPR rose during normotensive anesthesia in both groups to 1691 dynes/sec/cm^{-5} (fig 1 and 2) ($p<0.01$, paired t-test). The rise in TPR accompanied the fall in cardiac index. Likewise, the rise in cardiac index and stroke volume with nitroprusside hypotension, paralleled the fall in the TPR to a mean of 743 dynes/sec/cm^{-5} ($p<0.01$, paired t-test) (fig 1). The TPR, cardiac index, and stroke volume returned to prehypotensive levels upon ending nitroprusside infusion. Thus, the rise in cardiac index encountered during nitroprusside-induced hypotension was accounted for solely

*Calculations were made on a Hewlett-Packard programmed computer Model 9810 A Cardiac-pulmonary PAC from the formula:

$$TPR = \frac{79.9 \times \text{mean blood pressure}}{\text{cardiac output}}$$

$$CI = \frac{\text{cardiac output}}{\text{body surface area}}$$

$$SV = \frac{\text{cardiac output}}{\text{heart rate}} \times 1000$$

†Mean value refers to the statistical MAP mean.

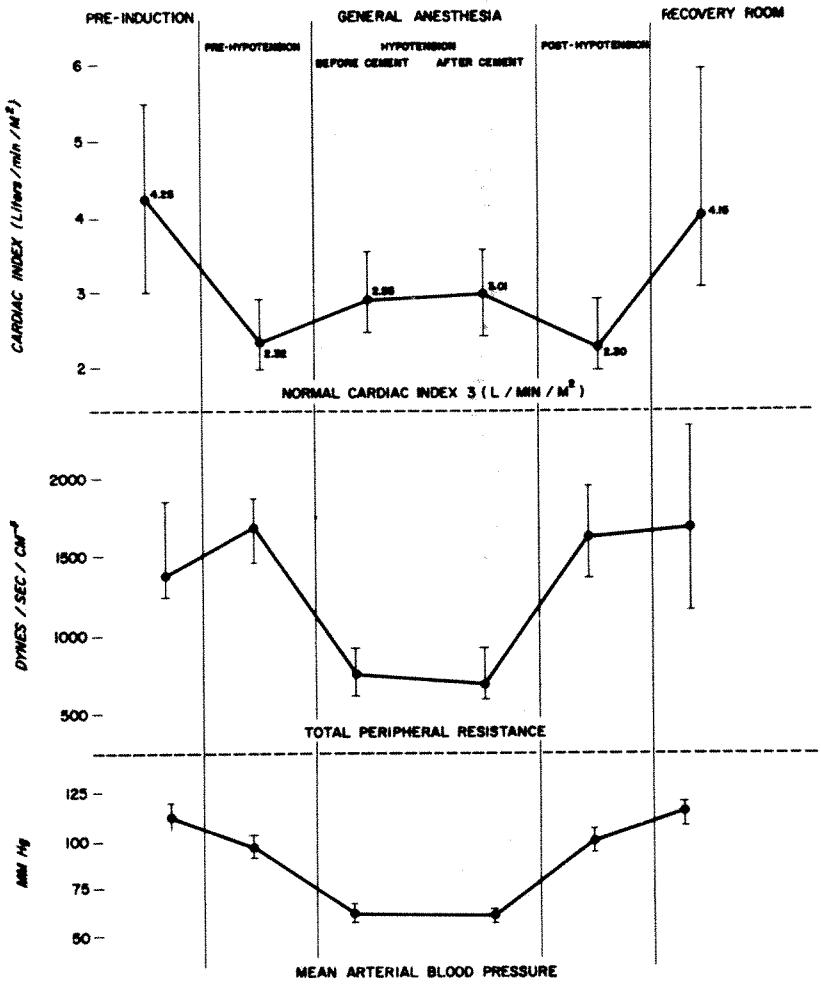


FIG 1. Cardiac index rose toward normal in all patients during nitroprusside administration under anesthesia ($p<0.01$). The mean TPR was markedly reduced during nitroprusside hypotension. The MAP achieving a dry surgical field was 64 mmHg. Isobars represent range of measured values.

by a marked decrease in the TPR. In contrast, there was little change in the cardiac index, stroke volume, or TPR (fig 2) in normotensive control patients. No significant change was noted in CI, TPR, or blood pressure in either group upon insertion of the acrylic cement into the femoral shaft.

Blood Gases and Tissue Perfusion.—A marked increase in A-aDo_2 was noted during hypotension in 8 patients but the Pao_2 was never less than 100 torr when an FIo_2 of 0.5 was maintained. However, arterial oxygenation returned to prehypotensive levels within minutes after resumption of normotension. Acid-base balance remained normal throughout the hypotensive period and no acidosis was noted. The urine output in both study groups remained normal. Enhanced tissue perfusion was further evident during hypotension in that the patients' skin became flushed and warmer to touch under the influence of nitroprusside. As a result, temperature loss was significant and troublesome during hypotension in the laminar airflow operating room. Hypotensive patients lost an average of 2.1° C temperature as compared with 0.5° C for controls ($p<$ 0.01, paired t-test).

Blood Loss.—The actual operating time averaged 105 ± 15 minutes for both groups. The duration of hypotension averaged 90 ± 15 minutes. The average blood loss in the 13 study patients was 475 (± 100) ml compared to 1475 (± 200) ml for controls (fig 5). The average preoperative hemoglobin in the hypotensive patients was 13.5 (range 10.8 to 15.8) gm/100 ml. The lowest postoperative hemoglobin in this group, usually

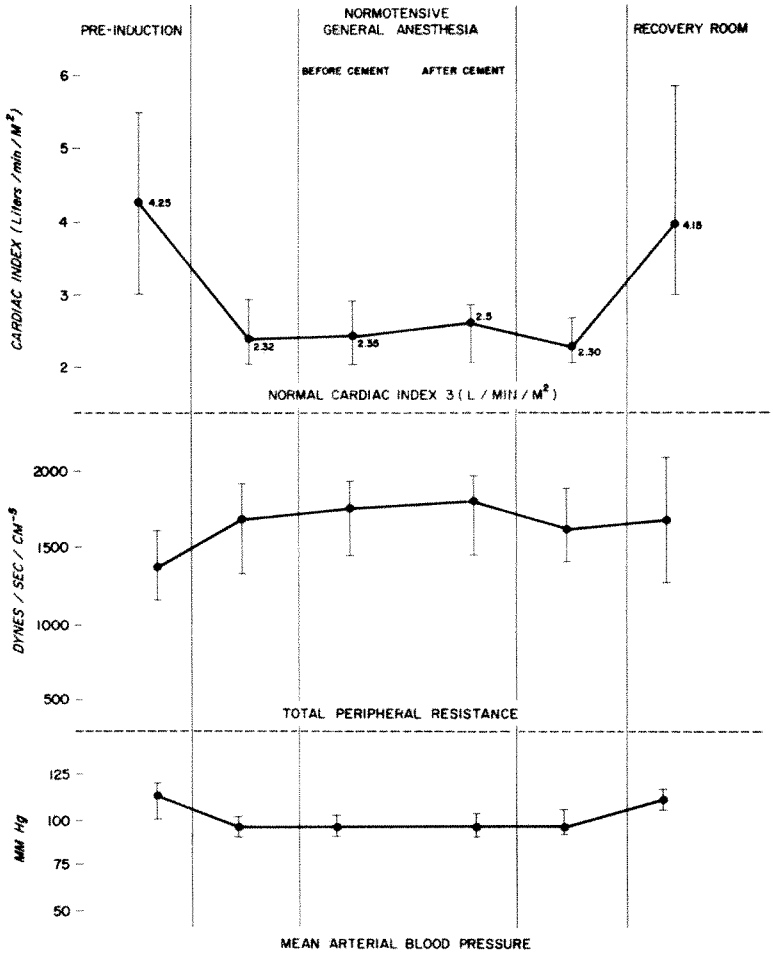


FIG 2. Cardiac index remained depressed in patients during normotensive halothane anesthesia. The mean TPR did not change significantly. The MAP was 98 torr. Isobars represent range of values measured.

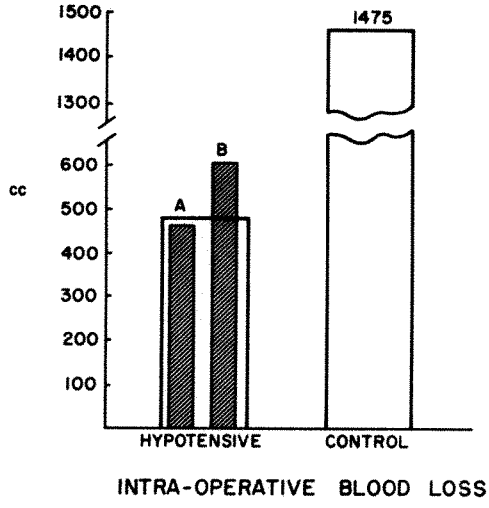


FIG 3. Surgical blood loss was significantly reduced with hypotensive anesthesia. Within the hypotensive group, patients without previous hip surgery (group A) lost less blood than those who had had previous hip surgery (group B).

found on the 3rd postoperative day, was 10.2 gm/100 ml.

Further, the amount of blood loss noted in the hypotensive study was divided into 2 distinct groups. Patients who had previous hip surgery lost significantly more blood than those without previous hip surgery. Nine patients who had no previous hip surgery lost an average of 460 ml of blood—31 percent of the expected blood loss. Four patients with previous hip surgery lost an average of 600 ml during hypotensive operation—45 percent of the expected loss. An extended surgical procedure was not a factor. The 5 control patients received a total of 14 units of homologous blood. Although homologous blood could not be given to the study patients, none was physiologically required.

Dosage of Nitroprusside.—The onset of action of nitroprusside began within 60 to 90 seconds after starting the infusion. The

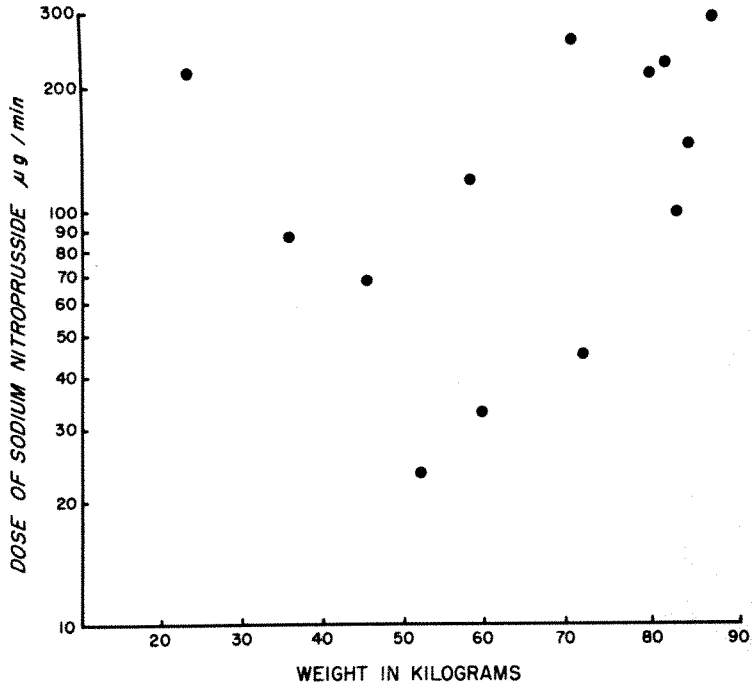


FIG 4. No correlation appears between patient weight and nitroprusside minute dosage needed for comparable levels of hypotension.

duration of action was equally evanescent, necessitating a controllable means of constant rate infusion to maintain stable hypotensive levels, blood pressure varying directly with the amount of nitroprusside infused. However, no consistent correlation could be found between dosage of nitroprusside and patient weight (fig 4), larger patients sometimes requiring the least drug. There was a noticeable inverse relationship between age

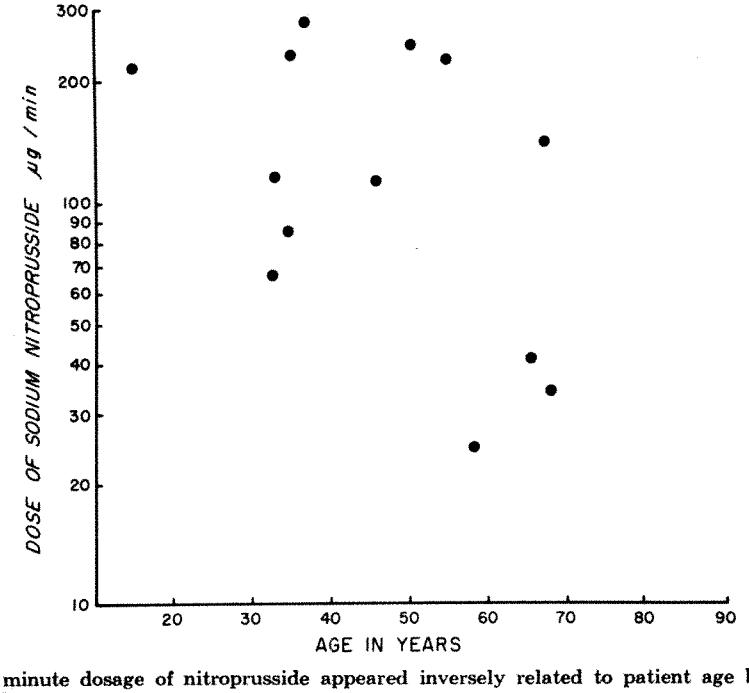


FIG 5. The minute dosage of nitroprusside appeared inversely related to patient age but was not statistically significant.

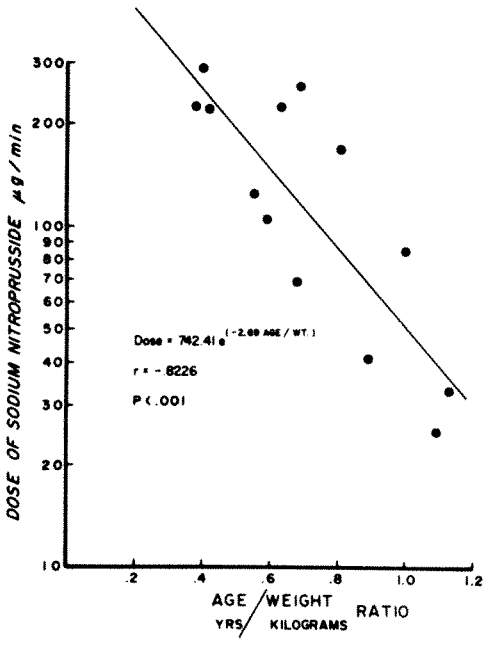


FIG 6. Age/weight ratios (yr/kg) produced a highly significant dose-response curve to maintain comparable levels of hypotension.

and the amount of the drug required but the correlation was not statistically significant (fig 5). There was, however, a highly significant correlation between the age/weight ratio of a given patient and the dose of nitroprusside required to maintain comparable levels of constant hypotension in another patient. Age/weight ratio (yr/kg) plotted against the required minute dosage of nitroprusside produced a highly significant ($p < 0.001$, $r = -0.822$) curve (fig 6). No nitroprusside tachyphylaxis was noted throughout the series. Once the desired level of blood pressure was attained and the minute dosage adjusted, only minor changes in the rate of infusion were required to maintain constant levels of hypotension. No adverse effects occurred as a result of sodium nitroprusside-induced hypotension.

DISCUSSION

To date, all methods of producing deliberate hypotension during anesthesia have caused a reduction in cardiac output in proportion to the degree of hypotension.[1] These methods include the popular combination and sequence of deep halothane anesthesia, positioning, positive-pressure ventilation, and ganglion blockers. Prys-Roberts and associates[10] presented convincing evidence that hypotension produced by halothane, whether deliberate or unintentional, is due to a dose-dependent impairment of myocardial contractility and not the result of vasodilatation, as popularly believed. Although vasodilatation may occur in selective vascular beds, the overall peripheral vascular resistance remains unchanged.

Admittedly, calculated values for TPR may not be meaningful when both pressure and cardiac output change in the same direction. However, our results confirmed those of Prys-Roberts. The calculated TPR remained essentially unchanged, if not slightly increased, throughout normotensive halothane anesthesia as compared with *awake* control measurements (fig 2). Simultaneously, the decreased cardiac output seen with halothane anesthesia is caused not only by a decrease in myocardial contractility but also is aggravated by a relative increase in workload, vascular resistance remaining unchanged.[11]

During nitroprusside-induced hypotension, the cardiac output increased toward normal from the depressed levels measured during normotensive anesthesia. The improvement in cardiac output and tissue perfusion was reflected entirely in decreased TPR. The reduction in myocardial afterload allowed the halothane-depressed myocardium to function at a more efficient level. Additionally, cardiac output returned to the lower prehypotensive levels following the end of nitroprusside infusion and return to normal vascular resistance (fig 1). Changes in heart rate and CVP were unrelated to changes in cardiac output. When such changes occurred, they were related more to the patient's state of hydration, a rise in heart rate or fall in CVP at the start of induced hypotension responding to fluid infusion without affecting the level of hypotension or cardiac output.

These conclusions are at variance with those of Wildsmith's group,[6] who also reported a 20 percent increase in cardiac output during nitroprusside hypotension but attributed the rise to a reflex and consistent increase in heart rate. The CVP fell significantly and the SV remained unchanged in their study. Rushmer[12] has demonstrated that tachycardia alone is not an efficient mechanism for increasing cardiac output unless such other mechanisms as increasing circulatory volume act to maintain or increase stroke volume.

Our fluid regimen followed that recommended by Jenkins and Giesecke[13] for hip operations. Therefore our patients received

substantial volume loading during the hour preceding deliberate hypotension. The British study, conducted on patients for middle-ear surgery, did not describe intraoperative fluid management. Perhaps differences in intraoperative fluid management account for the apparent discrepancy between this report and that of Wildsmith.

Like others,[4-7] our study indicates that use of sodium nitroprusside produces a hypotensive state clinically superior to other technics. The patient's skin became flushed and warm; urine output was not compromised; and no arterial or venous acidosis was noted during the hypotensive period. Nitroprusside hypotension significantly reduced surgical blood loss by reducing arterial blood pressure without apparent jeopardy to tissue blood flow. It acts directly on the arterioles, producing vasodilation and a hypotensive state unlike that produced by ganglion blockade.

Ganglion blockers have a highly specific action on synaptic transmission in autonomic ganglia which produces a number of troublesome side effects during induced hypotension. These effects include tachycardia, histamine release, cycloplegia, myoneural blockade, and tachyphylaxis,[1] although ganglion blockers differ in degree and type of side effects. Nitroprusside, in contrast, has no action on the heart or sympathetic ganglia.

The safety of nitroprusside-induced hypotension has been ascribed not only to improvement in tissue perfusion during hypotension but also to its evanescent action.[6,7] The speed of onset and the duration of action of nitroprusside is between 60 and 120 seconds, necessitating a continuous infusion to maintain steady hypotension. The degree to which nitroprusside lowers blood pressure is dose dependent, and pressure levels can be changed within seconds by altering the infusion rate, yet just such variability has constituted one of the main difficulties in its administration, dosage during anesthesia having usually been adjusted empirically according to response. The recommended dosage producing the desired pressure levels, around 70 to 75 torr systolic, has ranged from 0.5 to 30 μg/kg/min.[5]

As shown above, when both age *and* weight were considered, a highly significant dose-response curve relating the dose of nitroprusside to blood pressure decrease resulted (fig 6). Studies are in progress to further verify the relationship between age and weight to the predicted minute dosage of nitroprusside. Present findings suggest that perhaps age is the more important consideration.

Taylor[7] and Davies[14] have noted that young patients require larger doses of nitroprusside than adults to produce the same degree of hypotension. Our tentative dose-response curve confirms that observation. The age/weight ratio of a normally developing child from age 2 until maturity remains constant at around 0.3 to 0.5. A ratio of 0.35 (fig 6) on the curve would indicate that the needed dose of nitroprusside under halothane anesthesia would be in the range of 250 to 300 μg/min throughout childhood and adolescence.

Side Effects.—Doubts have been expressed about the safety of nitroprusside because its immediate metabolic products are cyanide and thiocyanate. Vesey's group[15] reported a significant rise in plasma cyanide following infusion of nitroprusside for hypotensive anesthesia. They concluded, however, that those levels encountered did not produce toxic effects. Certainly, nitroprusside has been safely used for extended periods in treating hypertensive crises, without a dangerous buildup of toxic products.[16] Recently, several anesthetic deaths[17-19] were reported in which nitroprusside was implicated, but most of these occurred under extraordinary circumstances in which the evidence against nitroprusside may be spurious.

Only Davies and coworkers[17] clearly documented a death due to nitroprusside overdose. Johnson[8] stated the therapeutic index of nitroprusside to be around 10:1, but McDowell and colleagues,[20] working with primates, suggested that the toxic:therapeutic dose ratio might be closer to 6:1. Too, the accumulation of toxic byproducts is related not only to total dosage but also to the time over which it is administered. Seifen* reported the successful use of nitroprusside for prolonged hypotensive anesthesia for the excision of a massive cerebral arteriovenous fistula. Mean blood pressure was kept at 65 torr for over 8 hours using 57,000 μg (119 μg/min) without clinical evidence of toxicity. The patient in the fatality reported by Davies, on the other hand, received 120 μg/kg/min (4800 μg/min) over 80 minutes. This patient, whose age/weight ratio was

*Seifen A: Prolonged deliberate hypotension with sodium nitroprusside: a case report. Presented at the 69th Annual Meeting of the Southern Medical Association, Miami Beach, Florida, November 16, 1975.

0.35, received 20 times the dose of nitroprusside our data would have predicted.

The goal of hypotensive anesthesia is the safe reduction of intraoperative blood loss, thus reducing transfusion risks. Previous hypotensive technics had a narrow margin of safety in that cardiac output was usually reduced in proportion to the degree of induced hypotension. This is in contrast to the results of our study, in which sodium nitroprusside was used as the sole hypotensive agent. Nitroprusside, a potent direct vasodilator, reduces the afterload on the anesthesia-depressed heart. The improvement in cardiac output plus better tissue perfusion appears to widen the margin of safety over that of earlier technics. We found not only that sodium nitroprusside dosage is predictable but also that this agent is effective and safe in reducing blood loss in selected patients undergoing total hip replacement in the supine position.

REFERENCES

1. Larson AG: Deliberate hypotension. Anesthesiology 25:682-706, 1964

2. Baker RJ, Moinichen SL, Nyhus LM: Transfusion reaction: a re-appraisal of surgical incidence and significance. Ann Surg 169:684-693, 1969

3. Moraca PP, Bitte EM, Hale DE, et al: Clinical evaluation of sodium nitroprusside as a hypotensive agent. Anesthesiology 23:193-199, 1962

4. Ross G, Cole PV: Cardiovascular actions of sodium nitroprusside in dogs. Anaesthesia 28:400-406, 1973

5. Styles M, Coleman AJ, Leary WP: Some hemodynamic effects of sodium nitroprusside. Anesthesiology 38:173-177, 1973

6. Wildsmith JAW, Marshall RL, Johnson JL, et al: Haemodynamic effect of sodium nitroprusside during nitrous oxide-halothane anaesthesia. Br J Anaesth 45:71-74, 1973

7. Taylor TH, Styles M, Lammins AJ: Sodium nitroprusside as a hypotensive agent in general anaesthesia. Br J Anaesth 42:859-893, 1970

8. Johnson CC: The actions and toxicity of sodium nitroprusside. Arch Int Pharmacodyn Ther 35:480-496, 1929

9. Guiha NH, Cohn JN, Mikulic E, et al: Treatment of refractory heart failure with infusion of nitroprusside. N Engl J Med 291:587-592, 1974

10. Prys-Roberts C, Lloyd JW, Fisher A, et al: Deliberate profound hypotension induced with halothane: studies of haemodynamics and pulmonary gas exchange. Br J Anaesth 46:105-116, 1974

11. Alper MH, Flacke W: Halothane and cardiac work. Anesthesiology 24:121, 1963

12. Rushmer RF: Cardiac output, Cardiovascular Dynamics. Philadelphia, WB Saunders Company, 1970, chapter 3, pp 70-112

13. Jenkins MT, Giesecke AH: Balanced salt solutions in clinical anesthesia, Refresher Courses in Anesthesiology. Philadelphia, JB Lippincott Company, 1974, 2:107-116

14. Davies DW, Greiss L, Kadar D, et al: Sodium nitroprusside in children: observation of metabolism during normal and above responses. Can Anaesth Soc J 22:553-560, 1975

15. Vesey CJ, Cole PV, Linnel JC, et al: Some metabolic effects of sodium nitroprusside in man. Br Med J 2:140-142, 1974

16. Gifford RW: Hypotensive emergencies and their treatment. Med Clin North Am 45:441-452, 1961

17. Davies DW, Kadar D, Steward DJ, et al: A sudden death associated with the use of sodium nitroprusside for induction of hypotension during anaesthesia. Can Anaesth Soc J 22:547-552, 1975

18. Merrifield AJ, Blundell MP: Toxicity of sodium nitroprusside. Br J Anaesth 46:324, 1974

19. Jack RD: Toxicity of sodium nitroprusside. Br J Anaesth 46:952, 1974

20. McDowell DG, Keaney NP, Turned JM, et al: The toxicity of sodium nitroprusside. Br J Anaesth 46:327-372, 1974

Train-of-Four Fade and Edrophonium Antagonism of Neuromuscular Block by Succinylcholine in Man

CHINGMUH LEE, MD*

Thumb twitch in response to train-of-four stimulation (2 Hz for 2 sec) of the ulnar nerve was measured in 36 patients anesthetized with halothane and N_2O and paralyzed with succinylcholine chloride (SCC). Train-of-four fade was detected whenever a block was produced. The train-of-four ratio decreased with continued exposure to SCC. Edrophonium effect was predictable by the train-of-four ratio in a semiquantitative manner, a high ratio predicting block enhancement and a low ratio, antagonism. When calculated at 30 to 50 percent recovery (from complete block), a train-of-four ratio of 0.4 or less reliably predicts antagonism. The magnitude of antagonism is also predictable in a semiquantitative manner, although complete antagonism cannot be ascertained. The lower the ratio, the more effective the antagonism becomes. Train-of-four fade, therefore, appears to be a consistent and sensitive quantitative sign of phase II neuromuscular block by SCC in man.

SENSITIVITY of neuromuscular transmission to nondepolarizing block is closely dependent on the rate of nerve stimulation. After establishment of a partial block, a train of indirectly-elicited twitches fade initially, reaching a new lower steady level at the 4th to 6th twitch.[1-3] The limit of fading corresponding to the frequency of stimulation is therefore well approximated by the train-of-four ratio, the ratio of 4th:1st twitch in each train. Train-of-four fade appears to be a consistent and sensitive quantitative sign of nondepolarizing block.[1-3]

Originally, train-of-four twitches at 2 Hz were observed to fade significantly under nondepolarizing block but not under depolarizing block.[1-3] Subsequently, fading was seen also after prolonged exposure to succinylcholine chloride (SCC).[4] Demonstration of phase II neuromuscular block, however, does not necessarily predict the antagonistic effect of anticholinesterases on the block. This report concerns the predictability, by the train-of-four ratio, of the effect of edrophonium, an anticholinesterase, on SCC-induced neuromuscular block.

METHODS

Thirty-six adult patients, 19 to 77 years old (ASA I or II) undergoing general surgical, gynecologic, and orthopedic operations, were studied. All had normal blood chemistries and were not receiving antibiotics, anticholinesterases, or other drugs known to affect neuromuscular transmission. Premedication consisted of 100 mg of pentobarbital, 75 mg of meperidine, and 0.6 mg of atropine IM at ½ to 1 hour before induction. Anesthesia was induced with 100 to 500 mg of thiopental IV (in increments) and maintained with halothane (0.3 to 1%, inspired) and N_2O-O_2 (60:40). All patients were intubated. Ventilation was controlled with a ventilator delivering tidal volumes of

*Assistant Professor, Department of Anesthesiology, UCLA, Harbor General Hospital Campus, Torrance California 90509.

Part of the material in this report was presented as an abstract at the 1974 ASA meeting, Washington, DC, and appeared in the Proceedings (pp 137-138) as "Quantitative assessment of dual block using train-of-four stimulation." That portion of this investigation was carried out at the Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina.

Paper received: 8/11/75

Accepted for publication: 1/27/76

12 ml/kg at the rate of 10 breaths/min. Body temperature was 36 to 37.5° C esophageally.

The procedure was that of stimulating the ulnar nerve and recording the thumb twitch.[4] Trains of 4 supramaximal square pulses of 0.1 ms duration (0.5 sec apart) were repeated every 12 seconds. The stimuli were derived from a Grass S88 stimulator, passed through a Grass SIU5 stimulus isolation unit and delivered close to the ulnar nerve via a pair of stainless needles placed subcutaneously at the wrist. Thumb twitch was recorded on a Grass Model 7 polygraph via a Grass FT.03 or FT 10C force-displacement transducer. The thumb was uniformly abducted. When an FT.03 was employed, tetanic force was not measured.

The initial dose of SCC, given IV, varied from 2 mg (as a test observation) to 90 mg as a bolus. Paralysis was maintained by IV drip of a 0.2 percent SCC solution, interrupted from time to time to assess the spontaneous recovery, the train-of-four ratio, and, occasionally, the effect of 10 or 15 mg of edrophonium IV.

Atropine (0.6 to 1 mg) routinely preceded edrophonium test. Train-of-four ratio was calculated at approximately 30 to 50 percent recovery from complete block and correlated with the effect of edrophonium. Since spontaneous recovery rate ranged from near nil to double the twitch tension within 30 seconds, the edrophonium effect was evaluated 30 to 40 seconds after injection. Invariably, the peak effect of edrophonium was obtained within this period.

RESULTS

The train-of-four ratio varied with the degree of block, the time course of each dose, and the total dose as well as the total duration of SCC exposure. The effect of edrophonium varied accordingly.

A high train-of-four ratio predicted block enhancement, while a low train-of-four ratio predicted antagonism (fig 1). If the 4th twitch was similar to the first in strength, block was enhanced; if much weaker than the first, block was antagonized. If the train-of-four ratio before the test was 0.3 to 0.4 or less, block was not enhanced but consistently antagonized.

Marked antagonism, equivocal effect, and block enhancement by edrophonium, was seen with various train-of-four ratios (fig 2). Such antagonizing effects were observed both in the train-of-four ratio, selectively improving the 4th twitch, and in the percentage of block, improving all twitches (fig 2, C). A slight antagonism might improve only the 4th and 3rd twitches of the train.

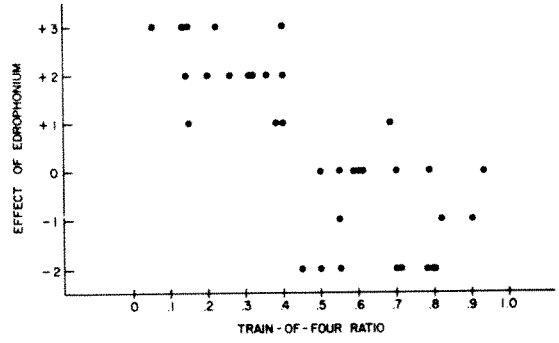


FIG 1. Relations between effect of edrophonium and the train-of-four fade in humans partially recovering from SCC neuromuscular block. Each dot represents 1 of the 35 observations made on 23 patients after SCC administration. Ordinate: −2, enhancement of block; −1, decrease in rate of recovery, without enhancement of block; 0, no apparent effect; +1, slight antagonism, or antagonism observable only in 4th and 3rd twitches of the train-of-four; +2, moderate antagonism, more than tripling 1st twitch of train-of-four in 30 to 40 seconds (converting 1st twitch from 20% to 70% of control); +3, marked antagonism, with complete reversal of 1st twitch of train-of-four. Note that no deepening of block occurred when train-of-four ratio was less than 0.4.

In some patients in whom both tetanic fade and post-tetanic twitch facilitation were clearly demonstrated, the block was not antagonized in the presence of a train-of-four ratio of 0.5, as illustrated in figure 3.

The total amount of SCC administered at the time of edrophonium tests averaged 6.06 ± 2.8 mg/kg, 3.18 ± 1.45 mg/kg, and 1.22 ± 0.72 mg/kg in the antagonized (16 observations), the unaffected (8 observations), and the enhanced (11 observations) occasions, respectively. These data do not represent the minimal dose requirement for each category.

DISCUSSION

Previously recognized clinical signs of phase II SCC block include lack of fasciculation, fade of tetanic contraction, and post-tetanic twitch facilitation. These signs do not emerge simultaneously;[5-10] they suggest changes in the nature of the block but, with probable exception of a marked post-tetanic

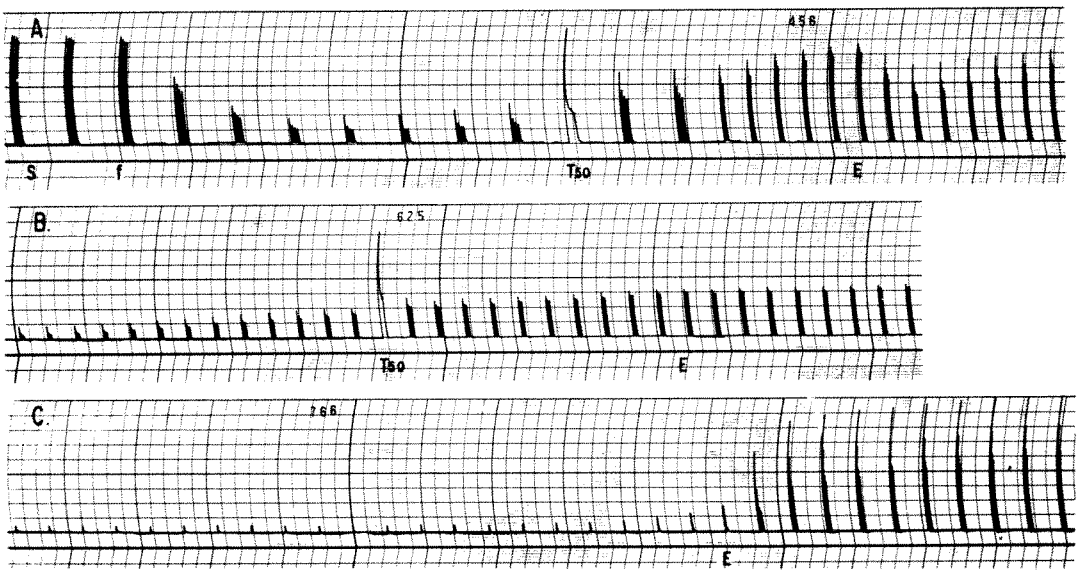


FIG 2. Three cases illustrating relationships among train-of-four fade, effects of edrophonium on block, and total quantity of SCC administered. Total SCC given was (A) 1.5 mg/kg, (B) 3 mg/kg; (C) 5 mg/kg. The train-of-four ratio (4th:1st twitch ratio in each train) measures train-of-four fade. In A and B, edrophonium (E, 10 mg IV) enhanced the block (A), or slowed down recovery (B) despite marked tetanic fade (T 50) and post-tetanic twitch facilitation. Train-of-four ratios before tetanic stimulations were 0.5 and 0.8, respectively. In (C), marked antagonism by edrophonium is seen in the presence of marked train-of-four fade. In A, "f" indicates fasciculations.

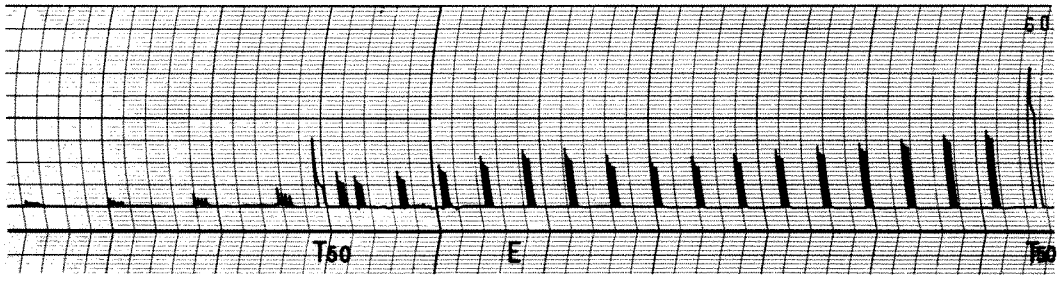


FIG 3. Block enhancement by edrophonium (E, 10 mg IV) despite faded tetanus (T 50) and marked post-tetanic twitch facilitation. Chart speed was varied before T 50 to permit clear tracing. Patient given an SCC total of 50 mg (0.6 mg/kg). The train-of-four ratio was 0.5 or more.

facilitation,[7] do not reliably predict antagonism by anticholinesterases. Difficulties have resulted from attempts to antagonize the block.[11-13]

Theoretically, an anticholinesterase can antagonize a curariform nondepolarizing block, produce neuromuscular block of its own, and prolong and/or enhance an SCC-induced depolarizing block.[14-17] Antagonism results when the overall antagonizing effect outweighs the enhancing effect, as often seen in phase II.

Our study demonstrated that train-of-four fade reliably predicts, in a semiquantitative manner, the overall effect of edrophonium on SCC-induced neuromuscular block. A slight train-of-four fade predicts block enhancement, a marked train-of-four fade, antagonism. The effect is unpredictable when the train-of-four ratio approximates 0.5. Until supported by further investigations, however, use of anticholinesterases cannot be routinely advocated for treatment of prolonged neuromuscular block after administration of large doses of SCC in clinical

practice, since the magnitude of antagonism may vary and may not be clinically satisfactory. Similar observation on prolonged neuromuscular block after SCC administration to patients with atypical plasma cholinesterase has been described.[18] Effects of other anticholinesterases have not been reported.

Whether train-of-four fade is manifestation of an underlying change in mechanism of neuromuscular block is not known. It is possible that each of the clinical signs of block (including train-of-four fade and tetanic fade), endplate polarization, and the sensitivity of the endplate to the transmitter may each change from the 1st to the 2nd phase with a different time course and dose relationship.

The existence of definite train-of-four fade following the 1st effective SCC dose was not seen by Ali's group,[1-3] who reported no train-of-four fade in the absence of halothane. A slight fade, however, may be suggestive of the beginning of a 2nd mechanism of block, ultimately characterized by marked train-of-four fade. My recent report[4] that train-of-four ratio permits clinical delineation of phases I and II, and the present observation that train-of-four ratio predicts edrophonium antagonism of SCC, support the speculation that train-of-four ratio reflects the moment-to-moment relative proportions of 2 mechanisms of SCC block operating simultaneously. The edrophonium-antagonizable block, characterized by marked train-of-four fade, becomes more observable as exposure continues.

During continuous SCC administration, train-of-four fade as a monitor of neuromuscular block has several potential advantages. It permits delineation of phases I and II.[4] Provided that 10 seconds are allowed between applications, the stimulation itself leaves no residual effect on the block or the fade and permits immediate reevaluation for dynamic studies. The ability to follow both the block and the fade simultaneously without artificially changing either (as does a tetanic stimulation) is a definite advantage in dealing with a short-acting neuromuscular blocker because the magnitude of fade, besides other factors, is dependent on the degree of block[19] (fig 2) which changes rapidly. Compared with tetanic stimulation, it is less painful and less likely to deplete the transmitter, thus introducing yet another factor in fade.

It is possibly more reliable than tetanic fade and post-tetanic facilitation in prediction of antagonism by edrophonium, although in the present study reliability of train-of-four and tetanus in prediction of edrophonium effect cannot be compared statistically because tetanic stimulation was purposely avoided in most cases.

ACKNOWLEDGMENT

The author thanks Ronald L. Katz, MD, Professor and Chairman, Department of Anesthesiology, UCLA School of Medicine, for reviewing and criticizing the manuscript during its preparation, and Ms. K. Hayes, for her excellent, untiring secretarial assistance.

REFERENCES

1. Ali HH, Utting JE, Gray TC: Quantitative assessment of residual antidepolarizing block (part I). Br J Anaesth 43:473-477, 1971

2. Ali HH, Utting JE, Gray TC: Quantitative assessment of residual antidepolarizing block (part II). Br J Anaesth 43:478-485, 1971

3. Ali HH, Utting JE, Gray TC: Stimulus frequency in the detection of neuromuscular block in humans. Br J Anaesth 42:967-978, 1970

4. Lee C: Dose-relationships of phase II, tachyphylaxis, and train-of-four fade in suxamethonium-induced dual neuromuscular block in man. Br J Anaesth 47:841-845, 1975

5. Churchill-Davidson HC, Christie TH, Wise RP: Dual neuromuscular block in man. Anesthesiology 21:144-149, 1960

6. Wylie WD, Churchill-Davidson HC: A Practice of Anaesthesia. Third edition. Chicago, Year Book Medical Publishers, 1972, pp 827-829

7. Katz RL, Wolf C, Papper EM: The nondepolarizing neuromuscular blocking action of succinylcholine in man. Anesthesiology 24:784-789, 1963

8. Crul JF, Long GJ, Brunner EA, et al: The changing pattern of neuromuscular blockade caused by succinylcholine in man. Anesthesiology 27:729-735, 1966

9. Gissen AJ, Katz RL, Karis JH, et al: Neuromuscular block in man during prolonged arterial infusion with succinylcholine. Anesthesiology 27:242-249, 1966

10. DeJong RH, Freund FG: Characteristics of the neuromuscular block with succinylcholine and decamethonium in man. Anesthesiology 28:583-591, 1967

11. Harper JK: Prolonged respiratory paralysis after succinylcholine (correspondence). Br Med J 1:866, 1952

12. Abrams MW, Ginsberg H: Prolonged apnoea following the use of suxamethonium. Anaesthesia 15:265-272, 1960

13. Vickers MDA: The mis-management of suxamethonium apnoea. Br J Anaesth 35:260-268, 1963

14. Katz RL, Gissen AJ, Karis JH: The effects of hexafluorenium and edrophonium on the neuromuscular blocking actions of succinylcholine, decamethonium, inbretil, and d-tubocurarine. Anesthesiology 26:154-161, 1965

15. Katz RL: Neuromuscular effects of d-tubocurarine, edrophonium and neostigmine in man. Anesthesiology 28:327-336, 1967

16. Katz RL, Katz GJ: Clinical use of muscle relaxants, Advances in Anesthesiology: Muscle Relaxants. Edited by LC Mark, GM Papper. New York, Hoeber, 1967, chapter VI, p 9

17. Churchill-Davidson HC: Prevention, diagnosis, and treatment of prolonged apnoea. Br J Anaesth 32:384-387, 1960

18. Savarese JJ, Ali HH, Murphy JD, et al: Train-of-four nerve stimulation in the management of prolonged neuromuscular blockade following succinylcholine. Anesthesiology 42:106-111, 1975

19. Katz RL: Electromyographic and mechanical effects of suxamethonium and tubocurarine on twitch, tetanic and post-tetanic responses. Br J Anaesth 45:849-859, 1973

LEFT VENTRICULAR FUNCTION. Simultaneous comparisons of left atrial, pulmonary capillary wedge, pulmonary artery end-diastolic and central venous pressure were obtained in patients undergoing cardiac operations. Left atrial pressure was identical to pulmonary capillary wedge pressure and pulmonary artery end-diastolic pressure in 24 percent and 18.5 percent of the measurements, respectively. It was within ± 4 torr of the pulmonary capillary wedge pressure and end-diastolic pressure in 94.6 percent and 89 percent respectively. Technical problems with the Swan-Ganz catheter occurred in over 25 percent of patients. The authors conclude that wedge pressure is a more reliable indirect measurement of left atrial pressure than is the pulmonary artery end-diastolic pressure. There was no consistent correlation between central venous pressure and either indirect or direct indicators of left ventricular function. *(Humphrey CB, Oury JH, Virgilio RW et al: An analysis of direct and indirect measurements of left atrial filling pressure. J Thor Cardiovas Surg 71:643-647, 1976)*

Neutrophil Chemotaxis During and After General Anesthesia and Operation

THEODORE H. STANLEY, MD*
GARY E. HILL, MD†
MARY R. PORTAS, MTASCP‡
NANCY A. HOGAN, BA§
HARRY R. HILL, MD‖
Salt Lake City, Utah**

The neutrophil granulocytes of 43 patients undergoing general anesthesia and operation were examined to determine if altered function occurs during these procedures. Neutrophil chemotaxis, random migration, and total and differential leukocyte counts were determined immediately before anesthesia; after 35 to 60 minutes of anesthesia but before operation; 60 minutes after initiation of operation; and 60 minutes after operation. Anesthetic agents included 1 to 3.5% enflurane, 0.5 to 2% halothane, or 0.5 to 1.1 mg/kg of morphine plus N_2O-O_2 (60:40).

Neutrophil and total white blood cell counts were uninfluenced by any of the anesthetics; however, marked rises in both occurred during operation and persisted postoperatively after each of the anesthetic technics. Neutrophil chemotaxis was reduced an average of 36, 32, and 21%, respectively, by halothane, enflurane, and morphine before operation and 20, 10, and 5% intraoperatively. Preoperative reductions in chemotaxis were statistically significant after all anesthetics. However, only halothane produced a significant intraoperative reduction in chemotaxis. Postoperative neutrophil chemotaxis did not differ from control (preanesthesia) values after any of the anesthetics. Halothane and enflurane reduced leukocytic random migration before but not after operation. Morphine had no effect on random migration at any time. These data demonstrate that anesthesia impairs neutrophil function in man but that operation appears to reverse this depression.

EARLY polymorphonuclear responses to bacterial invasion in the body are critical in determining the outcome of an infection. It has been shown[1] that prompt infiltration of phagocytic cells into an area of bacterial invasion is essential if multiplication of the organisms is to be prevented. Unidirectional movement of leukocytes toward a chemotactic stimulus, neutrophil chemotaxis, is one of the mechanisms by which phagocytic cells are attracted to an area of bacterial invasion.[2,3] The influence of anesthesia and operation on leukocyte motility has not been adequately studied.

*Associate Professor of Anesthesiology.

†Fellow in Anesthesiology.

‡Medical Technologist.

§Research Specialist.

‖Assistant Professor of Pediatrics and Pathology of the University of Utah; Investigator, Howard Hughes Medical Institute.

**Departments of Anesthesiology and the Division of Clinical Immunology of the Departments of Pediatrics and Pathology, University of Utah College of Medicine, Salt Lake City, Utah 84132.

Read at the 50th Congress of the International Anesthesia Research Society, March 14-18, 1976, Phoenix, Arizona.

This study was supported in part by US Public Health Service Grant AM18354.

Paper received: 2/19/76
Accepted for publication: 3/26/76

This investigation was undertaken to determine the effects of general anesthesia and operation on neutrophil chemotaxis in man.

METHODS

After giving informed consent, 43 adult patients about to undergo elective orthopedic, gynecologic, plastic, or neurosurgical operations served as experimental subjects. Patients who had infection, extensive tumors, required a blood transfusion, or sustained significant hypotension during or immediately after the operation were excluded from the study.

Premedication, at 1.5 hours before operation, included a barbiturate (1 mg/kg) or diazepam (1 mg/10 kg), morphine (1 mg/10 kg), and atropine (0.05 mg/10 kg). Blood (9.5 ml) from a peripheral vein was obtained before anesthesia and added to 0.5 ml of a solution of beef lung heparin (1000 u/ml). Following this, an infusion of lactated Ringer's solution was started in an arm vein and standard blood pressure and precordial pulse rate monitoring initiated. Anesthesia was induced with a sleep dose of sodium thiopental (200 to 300 mg) IV and maintained with enflurane (1 to 3.5%), halothane (0.5 to 2%) or morphine (0.5 to 1.1 mg/kg), plus N_2O-O_2 (60:40). All patients were intubated after 15 to 19 minutes of anesthesia.

Twenty patients were given succinylcholine (1.5 mg/kg) for intubation; the remainder required no muscle relaxant. Some patients needed pancuronium (2 to 7 mg) for muscle relaxation intraoperatively, but this was not administered until a 2nd blood specimen was obtained and the operation had begun. Muscle relaxation was reversed postoperatively with atropine (1 to 1.5 mg) and neostigmine (3 to 6 mg), and patients were extubated and returned to the recovery room.

Additional blood specimens for neutrophil chemotaxis examination were obtained after 35 to 60 minutes of anesthesia (after a minimum of 20 minutes following intubation) and before operation; following 60 minutes of operation; and 60 minutes after operation. All blood specimens were also examined for leukocyte random migration and total and differential white blood cell (WBC) counts.

Leukocyte-Function Tests.

Chemotaxis.—Hill and coworkers' *in-vitro* method[2,4] was used for studying chemotaxis. Leukocyte-rich plasma was obtained by allowing the erythrocytes in the 10-ml heparinized blood specimens to settle over a 1-hour period. After determination of the number of polymorphonuclear leukocytes (PMNs) in the leukocyte-rich plasma, 0.1 ml of the suspension was diluted to 0.4 ml with tissue-culture medium 199, and the cells were deposited on 1 side of a 5-μ millipore filter using a Shandon cytocentrifuge.* The filters were immediately placed in a modified Boyden chamber† and a chemotactic stimulus was added to the attractant side. After incubation for 3 hours at 37° C, the migrant PMNs within the reticule of 10 random fields were counted (using a 10x ocular, 45x objective, and 5x 5-mm photo reticule). A chemotactic index was calculated by dividing the number of migrant PMNs by the total number of PMNs ($x10^6$) delivered to the starting side of the filter. This method of calculating the chemotactic index takes into account only the number of PMNs delivered to the filter and the number moving completely through the filter. It, therefore, measures intrinsic neutrophil chemotactic activity. The percentage or total number of mononuclear cells in the suspension does not affect the leukotactic index, and there is no association between the number of PMNs delivered to the filter and the leukotactic index. Chemotactic assays were made in triplicate.

Chemotactic Factors.—A bacterial chemotactic factor was prepared from a culture filtrate of *Escherichia coli* grown in medium 199 for 24 hours at 37° C. After passage through a 0.2-μ millipore filter, this factor was frozen at −70° C in 1-ml ampules. For each experiment, an ampule was thawed and diluted in medium 199, so that each ml of the solution contained 50 μl of the factor. A volume of 2 ml of this solution was added to the bottom or attractant side of the chemotactic chamber for each analysis. The same lot of filtrate was used throughout the study.

Random Motion.—Random motion of leukocytes was measured by determining the chemotactic index when no chemotactic stimulus was added to the attractant side of the modified Boyden chamber.

RESULTS

The 3 groups of patients were comparable

*Shandon Scientific Company, Sewickley, Pennsylvania.

†Neuroprobe Corporation, Bethesda, Maryland.

with respect to age and weight and had operations of similar type and duration (table 1). Preanesthesia PMN chemotaxis, random migration and counts, and total WBC counts were also similar in the 3 groups (tables 2, 3). Neutrophil and total WBC counts were uninfluenced by any of the anesthetic agents; however, marked rises in both occurred during operation and persisted postoperatively after each of the anesthetic technics.

Neutrophil chemotaxis was reduced an average of 36, 32, and 21%, respectively, by halothane, enflurane, and morphine preoperatively and 20, 10, and 6% intraoperatively (table 3). Preoperative reductions in chemotaxis were statistically significant after all anesthetic agents (table 3). However, only halothane produced a significant intraoperative reduction in chemotaxis. Postoperative neutrophil chemotaxis was not significantly different from control values with any of the anesthetics.

Halothane and enflurane reduced preoperative but not intraoperative or postoperative random PMN migration (table 3).

TABLE 1
Preoperative and Intraoperative Data
(Mean ± SD)

	Halothane	Enflurane	Morphine
Number of patients	18	15	10
Age, years	43.6 ± 11.2	43.0 ± 12.7	40.3 ± 9.4
Weight, kg	64.5 ± 13.2	66.8 ± 10.7	64.2 ± 11.1
Duration of anesthetic prior to operation, min	42 ± 6	41 ± 6	44 ± 7
Duration of operation, min	183 ± 29	174 ± 21	198 ± 22

TABLE 2
Effects of Anesthesia on Total and Polymorphonuclear WBC Counts
(Mean ± SD)

	Anesthetic	Preanesthetic	Anesthesia	Anesthesia and operation	Postoperative
Total WBC count x 10^3 per mm^3	Halothane	8.4 ± 1.9	9.9 ± 2.7	16.1* ± 2.9	21.2† ± 3.6
	Enflurane	8.6 ± 1.4	8.4 ± 2.6	13.6* ± 2.1	19.7† ± 3.0
	Morphine	7.7 ± 1.6	8.9 ± 2.1	12.5‡ ± 2.3	13.0* ± 2.0
Polymorphonuclear cell count x 10^3 per mm^3	Halothane	4.0 ± 0.7	5.3 ± 1.4	10.5* ± 1.5	14.8† ± 2.3
	Enflurane	3.8 ± 0.8	3.9 ± 0.8	8.1* ± 1.3	13.0† ± 1.9
	Morphine	4.1 ± 0.5	5.6 ± 0.9	8.7‡ ± 1.4	9.3‡ ± 1.7

*$p<0.025$.
†$p<0.01$, Student's paired t-test.
‡$p<0.05$.

TABLE 3
Effects of Anesthesia on Leukocyte Chemotaxis and Random Migration
Means Chemotactic Index ± SD

Cell function	Anesthetic	Preanesthetic	Anesthesia	Anesthesia and operation	Postoperative
Chemotaxis	Halothane	76 ± 16	49* ± 10	61† ± 15	70 ± 19
	Enflurane	77 ± 13	52* ± 9	69 ± 13	75 ± 24
	Morphine	84 ± 15	66† ± 12	79 ± 14	90 ± 23
Random migration	Halothane	10.8 ± 2.7	6.4† ± 2.0	9.1 ± 2.5	9.5 ± 3.4
	Enflurane	10.5 ± 2.3	6.7† ± 1.6	8.7 ± 2.4	10.9 ± 3.2
	Morphine	11.4 ± 2.4	10.1 ± 2.0	13.2 ± 3.0	13.2 ± 2.7

*$p<0.025$, Student's paired t-test.
†$p<0.05$.

Morphine did not change random PMN migration at any time.

DISCUSSION

The neutrophil response to bacterial invasion consists of an increased release of PMNs from bone-marrow reserves into the blood, margination of PMNs to the walls of blood vessels, diapedesis through blood vessel walls into infected tissues, movement of PMNs to the invading organisms, and phagocytosis.[3] Investigations of the influence of anesthesia on the total neutrophil granulocyte response to infection have been primarily concerned with phagocytosis.[5-8] These studies have demonstrated that general anesthesia has little effect on phagocytosis *in vitro*[5,7,8] but can depress leukocytic bacterial engulfment *in vivo*.[6]

Before phagocytosis can take place, PMNs are attracted by and migrate toward the infecting stimulus. This process of leukocyte chemotaxis is markedly stimulated during active bacterial infections but can be depressed by certain disease processes (diabetes mellitus, rheumatoid arthritis, and allergic diseases)[9-15] and by the administration of a number of pharmacologic agents (histamine, epinephrine, isoproterenol, and the prostaglandins).[16]

Because of the nonavailability of a good *in-vivo* model and the tediousness of *in-vitro* methods, the influence of anesthesia on leukocyte migration has not been intensively studied. Development of a technic employing a cytocentrifuge to sediment leukocytes directly on millipore filters appears to have eliminated some of the problems of previous *in-vitro* methods of measuring neutrophil chemotaxis.[4]

The present study demonstrates that clinical concentrations of halothane and enflurane plus N_2O, and anesthetic doses of morphine and N_2O impair neutrophil granulocyte chemotaxis in man, and that random motion is also depressed by these anesthetic agents. Interestingly, operation and the early postoperative period are associated with marked rises in PMNs and total WBC counts and a reversal of granulocyte function.

Why anesthesia with the above agents depresses PMN function, and operation reverses this depression, is not clear. However, the mechanism may be related to changes produced by these agents in intracellular concentrations of cyclic 3′,5′-adenosine monophosphate (cAMP), cyclic 3′,5′-guanosine monophosphate (cGMP), or both these nucleotides. Our recent work[16] has shown that intracellular cAMP and cGMP provide opposing regulatory influences on leukocyte chemotactic activity, and has demonstrated that incubation of PMNs with cAMP, or with agents that promote increased intracellular cAMP, inhibits leukocyte chemotaxis. In contrast, cGMP and compounds which promote increased intracellular cGMP concentration markedly enhance the leukotactic response.

The influence of anesthesia and of anesthesia and operation on intracellular cAMP and cGMP has not been extensively studied. However, Sprague's group[17] has shown that clinical concentrations of halothane and isoflurane (an isomer of enflurane) result in marked increases in intracellular cAMP in rat aortic-wall tissue. Similar changes in leukocyte cAMP would help explain the effects of anesthesia on leukocyte chemotaxis in this study. The effects of operation and early postoperative recovery on intracellular nucleotide concentrations are unknown. Such variables as type and depth of anesthesia, degree of trauma, and area and duration of operation markedly influence metabolic and endocrine responses intraoperatively and postoperatively and make study of intracellular nucleotide concentrations and leukotactic mechanisms extremely difficult.

Surgical stress, particularly postoperative stress, is associated with marked elevations in circulating catecholamines.[18] The alpha-adrenergic catecholamines markedly enhance PMN hemotaxis.[16] In contrast, beta-adrenergic stimulators produce a marked depression of the neutrophil response to the bacterial chemotactic factor.[16] Perhaps operation and the early postoperative recovery period in our patients were associated with a preponderance of alpha- rather than of beta-adrenergic stimulation.

The effects of anesthesia and of specific anesthetic agents on the incidence and magnitude of postoperative infections is unknown. Our findings, and those of others,[6] suggest that the anesthetic state should enhance the development of infections. Further studies are being conducted to determine the effect of various anesthetic and pharmacologic agents on neutrophil granulocyte chemotaxis. Such studies may lead to technics for pharmacologic modification of PMN function during anesthesia and surgical procedures.

REFERENCES

1. Miles AA, Miles EM, Burke J: The value and duration of defense reactions of the skin to primary lodgement of bacteria. Br J Exp Pathol 38:79-96, 1957

2. Hill HR, Gerrard JM, Hogan NA, et al: Hyperactivity of neutrophil leukotactic responses during active bacterial infection. J Clin Invest 53: 996-1002, 1974

3. Marsh JC, Boggs DR, Cartwright GE, et al: Neutrophil kinetics in acute infection. J Clin Invest 46:1943-1953, 1967

4. Hill HR, Hogan NA, Mitchel TG, et al: Evaluation of a cyto-centrifuge method for measuring neutrophil granulocyte chemotaxis. J Lab Clin Med 86:703-710, 1975

5. Rosenbaum KJ, Orkin F: The effects of halothane on in vitro phagocytosis. Abstracts of Scientific Papers, Annual Meeting of the American Society of Anesthesiologists, San Francisco, 1973, pp 71-72

6. Bruce DL: Effect of halothane anesthesia on experimental salmonella peritonitis in mice. J Surg Res 7:180-185, 1967

7. Cullen BF: The effect of halothane and nitrous oxide on phagocytosis and human leukocyte metabolism. Anesth Analg 53:531-536, 1974

8. Cullen BF, Hume RB, Chretien PB: Phagocytosis during general anesthesia in man. Anesth Analg 54:501-504, 1975

9. Hill HR, Saulo HS, Dettloff JL, et al: Impaired leukotactic responsiveness in patients with juvenile diabetes mellitus. Clin Immunol Immunopathol 3:395-403, 1974

10. Mowat AG, Baum J: Chemotaxis of polymorphonuclear leukocytes from patients with diabetes mellitus. N Engl J Med 284:621-627, 1971

11. Mowat AG, Baum J: Chemotaxis of polymorphonuclear leukocytes from patients with rheumatoid arthritis. J. Clin Invest 50:2541-2549, 1971

12. Hill HR, Quie PG: Raised serum-IgE levels and defective neutrophil chemotaxis in three children with eczema and recurrent bacterial infections. Lancet 1:183-187, 1974

13. Hill HR, Quie PG, Ochs HD, et al: Defect in neutrophil granulocyte chemotaxis in Job's syndrome of recurrent "cold" staphylococcal abscesses. Lancet 2:617-619, 1974

14. Hill HR, Estensen RD, Hogan NA, et al: Severe staphylococcal disease associated with allergic manifestations, hyperimmunoglobulinemia E and defective neutrophil chemotaxis. J Lab Clin Med (in press)

15. Hill HR, Hogan NA, Williams PB, et al: Recurrent staphylococcal abscesses associated with defective neutrophil chemotaxis and allergic rhinitis. Ann Intern Med (in press)

16. Hill HR, Estensen RD, Quie PG, et al: Modulation of human neutrophil chemotactic responses by cyclic 3',5'-guanosine monophosphate and cyclic 3',5'-adenosine monophosphate. Metabolism 24:447-456, 1975

17. Sprague DH, Yang JC, Ngai SH: Effects of isoflurane and halothane on contractility and the cyclic 3',5'-adenosine monophosphate system in the rat aorta. Anesthesiology 40:162-167, 1974

18. Oyama T: Catecholamines, Anesthetic Management of Endocrine Disease. Edited by R Frey, FS Kern, O Mayrhofer. New York, Springer-Verlag, 1973, pp 76-84

Guest Discussion

DAVID L. BRUCE, MD
Department of Anesthesia
Northwestern University
Chicago, Illinois

Dr. Stanley and coworkers have tackled the question of anesthetic influence on chemotaxis and have come up with data that are most interesting. A possible role of anesthesia in promoting infections was postulated as long ago as 1903,[1] and this question is still prompted by studies up to and including the one under discussion. Since resistance to infection, the original definition of immunity, involves a number of events on both cellular and humoral levels, information about anesthetic effect on chemotaxis is important. Migration of neutrophils to a site of bacterial invasion is the body's first line of defense.

The results of this present study indicate a suppression of neutrophil chemotaxis by general anesthetics, an effect antagonized to an extent by operation. If the anesthetic effect had just involved the cellular events secondary to stimulation by a chemotactic factor, random migration would have been spared. However, if the data are arranged in terms of percent change from baseline values (table), we see that the volatile agents depressed chemotaxis and random migration of these cells to the same extent.

Previous studies by one of this paper's coauthors, Dr. H. R. Hill, failed to demonstrate a cyclic-GMP effect on random leukocyte motility at concentrations that markedly enhanced the neutrophil chemotactic response.[2] It thus seems likely that the volatile anesthetics produced fundamental changes in the intracellular contractile proteins that cause cellular locomotion and that the present authors' hypothesis of cyclic nucleotide modulation of these changes is only speculative. Lymphocytic contents of cyclic-AMP have been measured and found not to be altered by halothane,[3] but that does not prove that Dr. Stanley's hypothesis is incorrect. It does require its substantiation by measurements of cyclic nucleotides in these stimulated neutrophils.

TABLE

Anesthetic Effects on Chemotaxis and Random Migration

	Preanesthetic, %	Anesthesia, %	Anesthesia and operation, %	Postoperative, %
Halothane				
Chemotaxis	100	64	80	92
Random migration	100	59	84	87
Enflurane				
Chemotaxis	100	67	89	97
Random migration	100	63	82	103
Morphine				
Chemotaxis	100	78	94	107
Random migration	100	88	115	115

It is fascinating to see, in these data, yet another example of depression of a physiologic function by anesthesia and subsequent surgical stimulation of the same function. Again, the balance between anesthesia and operation is involved. Implicit in such a balance is the necessity for operation, and one wonders what hazard is associated with general anesthesia administered for relatively painless diagnostic or very minor surgical procedures. Most patients have sufficient functional reserves of heart, lungs, kidneys, liver, and hematopoietic tissues that modest reductions from anesthesia are unimportant. Gross surveys of infection rates among surgical patients would likely show nothing. Studies like that reported today carry the implication that the patient with marginal reserves, such as one with granulocytopenia, will be further compromised by general anesthesia.

We do not "put patients to sleep;" we give potentially fatal, toxic drugs that facilitate operation but compromise virtually every physiologic function that has been studied. General anesthesia carries with it this real, apparently irreducible risk, and this requires that it be treated as controlled toxicity rather than a harmless period of sleep.

REFERENCES

1. Bruce DL, Wingard DW: Anesthesia and the immune response. Anesthesiology 34:271-282, 1971

2. Hill HR, Estensen RD, Quie PG, et al: Modulation of human neutrophil chemotactic responses by cyclic 3′,5′-guanosine monophosphate and cyclic 3′,5′-adenosine monophosphate. Metabolism 24:447-456, 1975

3. Bruce DL: Halothane action on lymphocytes does not involve cyclic-AMP. Anesthesiology 44: 151-154, 1976

DRUG INTERACTION. Methyldopa and haloperidol are both thought to prevent dopamine from reaching its central neurotransmitter effector site. As such, patients may become vulnerable to unwanted mental effects of methyldopa when it is combined with haloperidol. The authors describe two hypertensive patients treated with methyldopa who developed impaired mental and motor function when haloperidol was added to the regimen. Symptoms cleared within 48-72 hours after discontinuing haloperidol. *(Thornton WE: Dementia induced by methyldopa with haloperidol. N Engl J Med 294:1222, 1976)*

Hypertension and Decreased Renal Blood Flow Following Methylene Blue Injection

ALEXANDER A. BIRCH, MD*
WILLIAM H. BOYCE, MD†
Winston-Salem, North Carolina‡

Renal blood flow (RBF) and arterial blood pressure (BP) were monitored in 12 patients undergoing nephrolithotomy in the lateral flexed position. All patients were preoxygenated and were anesthetized with sodium thiopental, N_2O, O_2, and fentanyl. Maintenance relaxation was obtained with pancuronium bromide. Arterial pressure was monitored by percutaneous arterial catheter.

Following exposure of the kidney and renal pedicle, an electromagnetic flow probe was attached to the renal artery and baseline flows recorded. Following baseline measurements, 20 ml of 1 percent methylene blue was given intravenously. All patients studied showed an immediate rise in BP, and 11/12 showed a simultaneous decrease in RBF. The average fall in RBF was 35 percent at one minute. Both parameters returned to normal values on the average in 177 seconds. The decreased RBF appeared to be part of a generalized vasoconstriction caused either by sympathetic reflexes or by the direct action of methylene blue.

AT OUR institution, nephrolithotomies are frequently performed for removal of staghorn renal calculi. To facilitate entry into the kidney, a relatively avascular renal plane is located by the following procedure: The posterior segmental renal artery is located and clamped. Methylene blue (20 ml, 1% solution) is then given IV, the plane between the now blue kidney and the red distribution of the postsegmental artery is determined, and the kidney incision made along the intersection of the 2 colors.

While continuously monitoring arterial blood pressure (BP) and renal blood flow (RBF) for another project, we observed marked transient rises in BP and decreases in RBF after methylene blue injection. These observations prompted the following investigation.

METHODS AND MATERIALS

After informed consent, BP and RBF changes were studied in 12 adult male and female patients, aged 19 to 65 years. Premedication consisted of 10 mg of diazepam and 0.4 mg of atropine IM, 1 hour before induction of anesthesia. After preoxygenation (100% O_2), anesthesia was induced with sodium thiopental (3 to 4 mg/kg), N_2O, O_2, and fentanyl. Pancuronium or succinylcholine was used to facilitate intubation. Maintenance anesthesia was with N_2O, O_2, and fentanyl, and maintenance relaxation was with pancuronium.

A 20-gauge Teflon catheter was placed in either the right or left radial artery and attached to an arterial pressure transducer. All patients were intubated and turned to the flexed lateral position. Ventilation was controlled throughout the operation.

Blood loss during exposure of the kidney did not exceed 200 ml and was replaced with 5 percent dextrose in lactated Ringer's solution. Once the renal artery was exposed, a properly calibrated electromagnetic flow

*Associate Professor, Department of Anesthesia.

†Professor, Department of Urology.

‡North Carolina Baptist Hospital, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina 27103.

Paper received: 9/15/75
Accepted for publication: 2/5/76

probe* was placed around the artery and flow recorded. Signals from the flow probe and the transducer† were displayed on a Model-7 Grass Polygraph‡. After clamping the posterior segmental artery, baseline measurements were made; then 20 ml of 1 percent methylene blue was given over a 15-second period, the entire response period being recorded.

RESULTS

Thirty seconds after injection, the mean arterial pressure (MAP) of all patients had increased ($p<0.001$, sign test). At 1 minute, MAP was still significantly higher than baseline ($p<0.001$), as was the 2-minute value in 11/12 patients ($p<0.003$). At the 3-minute mark, MAP had returned to near baseline in all patients.

Following methylene blue injection, RBF fell in 11/12 patients at both the 30-second and 1-minute intervals ($p<0.01$). At one minute, the average RBF fell 35 percent. The RBF in 9/10 patients ($p<0.011$) was less than baseline at 2 minutes (fig 1), all patients tending to return toward baseline at 3 minutes.

Changes in renal vascular resistance at 30 seconds and 1 minute were also statistically significant ($p<0.001$, fig 2).

Five patients developed arrhythmias (either PACs or occasional PVCs) during the peak of the hypertensive response; these arrhythmias disappeared as the BP returned toward control values. Transient hypertension occurred in every patient studied and increases in BP were severe, with an average duration of 177 seconds (range 90 to 250). The range of peak values was from 185/105 to 260/155, one man showing a rise of 90 torr, from 170/110 to 260/155.

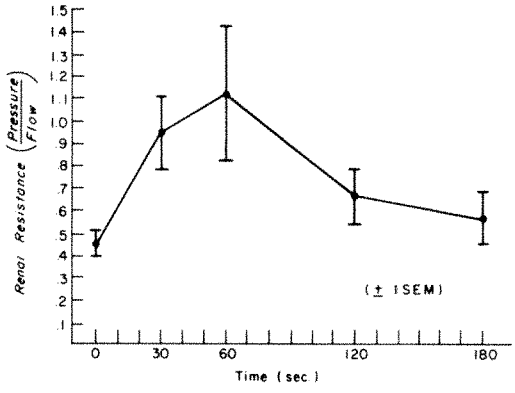


FIG 2. Changes in renal vascular resistance in 12 patients (± 1 SEM) following methylene blue injection.

DISCUSSION

Goodman and Gilman[1] mention a "moderate rise in blood pressure after methylene blue injection in animals," but we have found no prior report of this effect in man. In our study, MAP rose an average of 35 percent above baseline at 30 seconds and 29 percent at 1 minute. At the same time as hypertension occurred, a fall in RBF was seen, with an average decrease of 28 percent at 30 seconds and 35 percent at 1 minute, followed by a gradual return toward normal.

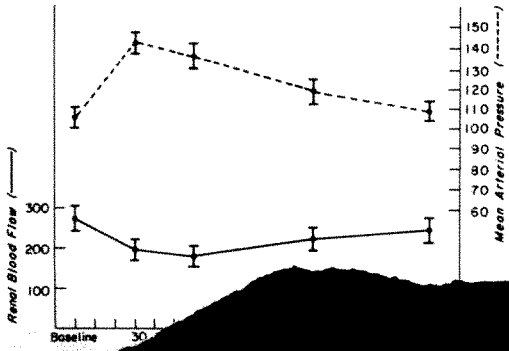
The acute onset of these changes along with a short duration (177 sec) suggests to us that methylene blue injection either causes a generalized reflex vasoconstriction or direct vascular effect. The hypertension evidently causes reflex slowing of the heart by stimulating sino-aortic baroreceptors.[2] We also feel that the arrhythmias were related to the hypertension.

The mechanism of action of methylene blue in causing vasoconstriction still remains [illegible]. The methylene blue used in [illegible] distilled-water solu-

*Carolina Medical Electronics, King, North Carolina.

†Statham Instruments, Inc, Oxnard, California.

‡Grass Instruments, Quincy, Massachusetts.



FIG

takes 5 to 15 minutes before sizable amounts are released, which does not coincide with the time course seen in our study. The role of serotonin, speed of drug injection, as well as of dosage, in methylene blue-induced hypertension and decreased RBF, require further study. Meanwhile, it is clinically important for anesthesiologists to be aware of these responses in man, so that blood pressure readings during such procedures will not lead to the conclusion that the patient is "light" and to the administration of an inappropriate dose of anesthetic or analgesics.

REFERENCES

1. Goodman LS, Gilman A: The Pharmacological Basis of Therapeutics. Fourth edition. New York, The Macmillan Company, 1970, pp 1056-1057

2. Detweiler DK: Circulation, Physiological Basis of Medical Practice. Ninth edition. Edited by JR Brobeck. Baltimore, The Williams & Wilkins Company, 1973, chapter 6, p 48

3. Schick PK, Yu BP: Methylene blue-induced serotonin release in human platelets. J Lab Clin Med 82:546-553, 1973

CPK-MB ISOENZYME. The diagnosis of acute myocardial infarction postoperatively may be obscured by anesthetic or analgesic drugs and nonspecific serum enzyme changes after major surgery. The electrocardiogram may fail to diagnose acute myocardial infarctions in over 30 percent of patients. However, the MB isoenzyme of creatinine phosphokinase (CPK) is specific for myocardium and may serve as an indicator of injury in the early postoperative period. CPK-MB isoenzyme was present in the serum in 10 of 30 patients after cardiopulmonary bypass and in no patient after thoracotomy. In 6 of these patients the other enzyme tests were not suggestive of myocardial injury. Isoenzyme elevations correlated with the duration of cardiopulmonary bypass (over 90 minutes), aortic cross clamp time (over 75 minutes), interruption of coronary artery blood flow for more than 30 minutes and heart valve replacement rather than vein bypass grafts. CPK-MB isoenzyme proved to be a useful adjunct in the diagnosis of acute myocardial infarction in the early postoperative period. *(Pyle RB, Blomberg DJ, Burke MD et al: CPK-MB isoenzyme: Use in diagnosis of acute myocardial infarction in the early postoperative period. J Thor Cardiovas Surg 71:884-890, 1976)*

Halothane MAC in Dogs Unchanged by Phenobarbital

OSCAR VIEGAS, MD*
ROBERT K. STOELTING, MD†
Indianapolis, Indiana

Halothane MAC in dogs was not significantly changed by phenobarbital (PB) therapy. Following 10 consecutive days of oral PB (10 mg/kg), halothane MAC was 0.95 ± 0.05 vol/dl (mean ± SE) compared with a halothane MAC of 1.05 ± 0.03 vol/dl in another group not given PB. The absence of change in MAC may reflect either the development of tolerance to CNS sedative effects of PB or the masking of antanalgesia effects of the barbiturate by associated sedation and/or analgesia.

ACCELERATED anesthetic drug biotransformation could prolong establishment of the brain partial pressure required for anesthesia (prolonged induction) but should not change the brain partial pressure necessary to produce anesthesia. However, any associated CNS sedative effects produced by agents responsible for accelerated drug biotransformation could have additive anesthetic effects which would be reflected by a reduced MAC for an inhalation anesthetic.

For example, phenobarbital (PB) pretreatment in rats stimulates hepatic microsomal enzymes responsible for inhalation anesthetic biotransformation[1] and at the same time is a CNS depressant.[2] Therefore, we speculated PB might reduce anesthetic requirements. However, this study demonstrates that PB administration did not significantly alter halothane MAC in the dog.

METHODS

Anesthesia was achieved and maintained in 12 mongrel dogs (10 to 15 kg), using halothane in O_2. Endotracheal intubation was performed without neuromuscular blockers and ventilation was then mechanically controlled. Esophageal temperature was monitored and external heating or cooling applied to maintain body temperature near 37° C. End-tidal halothane was measured intermittently with a Beckman infrared analyzer and maintained constant for 15 minutes. After 15 minutes and just before the first 30-second tail-clamp stimulus, an arterial blood sample was drawn from a femoral artery catheter for determination of arterial blood gases and pH, halothane,[3] and PB concentrations.[4]

The arterial halothane concentration was converted to the equivalent alveolar concentration assuming a halothane blood/gas partition coefficient equal to 2.4 for the dog. Halothane MAC was calculated as that concentration midway between the highest halothane concentration just permitting movement and the lowest concentration preventing movement.[5]

Six dogs received PB (10 mg/kg) orally every afternoon (1600 to 1800 hours) for 10 consecutive days. Halothane MAC was determined about 16 hours after the last PB dose. The 6 remaining dogs did not receive PB but were anesthetized in an identical manner.

*Assistant Professor of Anesthesia.
†Professor of Anesthesiology/Pharmacology.
‡Indiana University School of Medicine, Indianapolis, Indiana 46202.

Paper received: 11/7/75
Accepted for publication: 1/28/76

Data were analyzed for statistical significance by paired analysis with Student's *t*-test, and $p<0.05$ considered significant.

RESULTS

The presence of serum PB levels of 24.9 ± 3.8 μg/ml (mean ± SE) was not associated with a significantly reduced halothane MAC as compared with dogs not given PB (table). MAC in the treated dogs was 0.95 ± 0.05 vol/dl and in the untreated dogs 1.05 ± 0.03 vol/dl.

DISCUSSION

Although sedation may limit initial therapy with PB, the usual response is the development of tolerance despite the presence of therapeutic blood levels.[2] Indeed, it was our impression that animals treated with PB were not sedated as compared with the untreated group. Nevertheless, it seemed possible that CNS depression produced by PB, even in the absence of apparent sedation, might have an additive anesthetic effect as reflected by decreased MAC for an inhalation anesthetic.

However, when the last PB dose was given about 16 hours before anesthesia (simulating the patient taking PB chronically but not receiving the last dose before an elective operation), halothane MAC was not altered despite the presence of a serum PB concentration averaging 24.9 μg/ml (therapeutic range for seizure control 20 to 30 μg/ml*).

*Solow EB: Personal communication. Indiana University School of Medicine, Indianapolis, IN 46202.

TABLE

Halothane MAC and Serum Phenobarbital Concentrations

	Phenobarbital		No phenobarbital
	MAC, vol/dl	Serum PB, μg/ml	MAC, vol/dl
	0.92	18.2	1.01
	0.77	23.2	0.95
	0.90	40.4	0.98
	1.01	25.0	1.08
	0.92	29.0	1.05
	1.15	14.0	1.19
Mean	0.95	24.9	1.05
± SE	0.05	3.8	0.03
Pa_{O_2}, torr	289 ± 31		325 ± 28
Pa_{CO_2}, torr	34.4 ± 3.1		32.1 ± 2.5
pH	7.45 ± 0.1		7.41 ± 0.1

Drugs such as reserpine,[6] alpha-methyldopa,[6] and chronic dextroamphetamine[7] may decrease halothane MAC secondary to CNS catecholamine depletion. The effect of PB on CNS catecholamine levels is not known, but sedative doses do prevent the stress-induced release of norepinephrine in the brain stem of rats.[2]

The analgesic action of barbiturates is controversial. In 1 report,[8] pentobarbital was effective in reducing postoperative pain in 50 percent of patients. In contrast, Dundee[9] and Clutton-Brock,[10] independently, demonstrated that thiopental or pentobarbital reduced the pain threshold. If antanalgesia was indeed produced by PB, a greater halothane concentration would have been required to prevent movement in response to the painful tail-clamp stimulus. The fact that halothane MAC was not altered suggested that PB antanalgesia either did not occur or was offset by sedative and/or analgesic actions of the drug.

Anesthetic induction may be delayed in the presence of enzyme induction. Berman's group[11] reported that PB did not alter the arterial methoxyflurane concentration required to produce sleep, but the time required for establishment of this arterial concentration was delayed. In our study, the difficulty in maintaining an identical inspired anesthetic concentration, ventilation, and cardiac output, plus the inability to quantitate enzyme induction or demonstrate a clear endpoint for induction, made any attempt at measuring the time for anesthetic induction impractical.

If these data are applicable to man, we conclude that halothane anesthetic requirement will not be altered in the patient receiving PB.

ACKNOWLEDGMENT

The authors thank Elizabeth B. Solow, MS, for determining the serum phenobarbital levels.

REFERENCES

1. Brown BR: Hepatic microsomal enzyme induction. Anesthesiology 39:178-187, 1973

2. Maynert EW: Sedatives and hypnotics. II: Barbiturate, Drills Pharmacology in Medicine. Edited by JR DiPalma. New York, McGraw-Hill, 1974, pp 250-274

3. Jacobs ES: The gas chromatographic determination of halopropane in blood. Anesth & Analg 43:177-185, 1964

4. Solow EB, Green JR: The simultaneous determination of multiple anticonvulsant drug levels by gas-liquid chromatography. Method and clinical application. Neurology 22:540-550, 1972

5. Eger EI II, Saidman LJ, Brandstater B: Minimum alveolar concentration: a standard of anesthetic potency. Anesthesiology 26:756-763, 1965

6. Miller RD, Way WL, Eger EI II: The effects of alpha-methyldopa, reserpine, guanethidine and iproniazid on minimum alveolar anesthesia requirements (MAC). Anesthesiology 29:1153-1158, 1968

7. Johnston RR, Way WL, Miller RD: Alteration of anesthetic requirement by amphetamine. Anesthesiology 36:357-363, 1972

8. Keats AS, Beecher HR: Pain relief with hypnotic doses of barbiturates and a hypothesis. J Pharmacol Exp Ther 100:1-13, 1950

9. Dundee JW: Alterations in response to somatic pain associated with anaesthesia. II. The effect of thiopentone and pentobarbitone. Br J Anaesth 32:407-414, 1960

10. Clutton-Brock J: Pain and the barbiturate. Anaesthesia 16:80-88, 1961

11. Berman ML, Lowe HJ, Hagler KJ, et al: Uptake and elimination of methoxyflurane as influenced by enzyme induction in the rat. Anesthesiology 38:352-357, 1973

INSULIN ABSORBANCE. Interest in low-dose constant intravenous insulin infusion for the management of ketoacidosis has raised questions as to the method of insulin administration. A recent study showed greater than 50 percent insulin absorption to glass or plastic intravenous infusion containers. The authors evaluated 500 ml of normal saline and lactated Ringers (with or without 1.25 grams/dl human serum albumin) for insulin infusion. An infusion system utilizing a 50 ml "washout" with 25 units regular insulin permits delivery of at least 75 percent of the expected insulin for the first 50 ml and 100 percent thereafter. After the first 20 ml insulin concentrations were identical with or without added albumin. The passage of 50 ml through the infusion apparatus probably saturates insulin binding sites such that further insulin loss is minimal. *(Peterson L, Caldwell J, Hoffman J: Insulin absorbance to polyvinylchloride surfaces with implications for constant-infusion therapy. Diabetes 25:72-74, 1976)*

Massive Myoglobinuria Precipitated by Halothane and Succinylcholine in a Member of a Family with Elevation of Serum Creatine Phosphokinase

WILLIAM E. MOORE, MD*
ROBERT L. WATSON, MD†
JAMES J. SUMMARY, PhD‡
Honolulu, Hawaii§

Massive myoglobinuria developed in a patient given halothane and IV succinylcholine. Marked elevations of serum CPK were found in the patient and several family members. Myopathic changes in electromyogram and lack of neuromuscular symptoms and physical findings prompted the diagnosis of familial nonprogressive muscular dystrophy. Other hereditary muscular diseases were eliminated by medical workup. It is recommended that patients with known myopathy or unexplained elevations of serum CPK not receive the combination of halothane and succinylcholine.

MYOGLOBIN, along with other contents of skeletal muscle, can be released into the circulation in response to hereditary muscle disorders, muscle ischemia, and, rarely, from drugs and other toxins.[1] Authors of isolated case reports[2,3] of massive myoglobinuria implicating general anesthesia have failed to fully evaluate their patients postoperatively for the various hereditary muscle disorders known to be associated with myoglobinuria.

The following case is unique in that massive myoglobinuria secondary to halothane-succinylcholine general anesthesia occurred in a patient who was later found to have a subclinical myopathy characterized by persistently elevated serum creatine phosphokinase (CPK).

CASE REPORT

The patient was a healthy, 13-year-old, 32-kg boy, admitted for a repeat tympanoplasty 2 years after his initial operation, which had been complicated by postoperative infection.

Premedication was with 30 mg of meperidine, 50 mg of pentobarbital, and 0.15 mg of glycopyrrolate. Curare (3 mg IV) preceded induction with 150 mg of thiopental and 60 mg of succinylcholine. Neither gross muscle fasciculations nor myotonic response was noted; however, muscle relaxation was judged inadequate and the patient received a second bolus of 60 mg of succinylcholine. He was then intubated and maintained on 1 percent halothane and 60 percent N_2O. The operative procedure was completed uneventfully 2 hours later with no elevation of rectal temperature.

No complications were noted until 4 hours postoperatively, when the first voided urine was dark brown. Benzidine test of urine was positive for occult blood but the

*Assistant Chief, Anesthesia and Operative Service, Tripler Army Medical Center.

†Assistant Chief, Anesthesia and Operative Service, Brooke Army Medical Center, Fort Sam Houston, Texas.

‡Chief, Clinical Chemistry, Department of Pathology, Letterman Army Medical Center, Presidio, San Francisco.

§Anesthesia and Operative Service and Clinical Investigation Service, Tripler Army Medical Center, APO San Francisco, California 96438.

Paper received: 11/17/75
Accepted for publication: 1/29/76

urine contained no red blood cell forms. Spun serum was clear, so a presumptive diagnosis of myoglobinuria prompted treatment with IV fluid and furosemide diuresis. Hemoglobinuria was eliminated by ammonium sulfate precipitation. Diuresis was brisk but urine remained positive for myoglobin for 24 hours postoperatively. No renal failure resulted. The patient exhibited marked muscular weakness and required assistance in standing and walking for the first 2 postoperative days.

Clinical laboratory tests are summarized in the table. The extremely high levels of serum CPK were isoenzyme type III, characteristic of skeletal muscle.

Review of the patient's medical history revealed no prior episodes of dark urine and only minor complaints of calf muscle cramps with vigorous exercise. The previous anesthetic procedure had been by halothane mask induction with a single bolus of succinylcholine (1 mg/kg); the rectal temperature had been normal.

Family members, screened for CPK, showed abnormal elevations in the father and 3 of the 4 siblings. An 11-year-old brother had a serum CPK of 1000, with a repeat CPK 1 year later of 541; all CPK elevations were of the isoenzyme type III.

Because of the possibility of familial muscle disease, the propositus was reevaluated 4 months postoperatively for hereditary muscle diseases associated with myoglobinuria. Detailed neuromuscular examination showed no abnormalities. Blood lactic acid levels following ischemic forearm exercise were identical with those of a control volunteer. Gastrocnemius muscle biopsy specimens appeared normal to light and electron microscopy. Assay of muscle phosphorylase "b," using the method of Krebs and Fisher,[4] demonstrated 1.56 μ/mg protein in the patient and 0.31 μ/mg protein in control human volunteer muscle. Rowland's group[5] previously reported no detectable phosphorylase "b" activity in patients with McArdle's disease.

Serum triglycerides were normal. Electromyogram (EMG) showed decreased amplitude and duration compatible with a myopathic process. An EMG 1 year postoperatively gave the same results. An EMG on the brother with elevated CPK levels was also compatible with myopathy.

Lack of muscular symptoms and physical findings is strong evidence against periodic paralysis, myotonia dystrophica, and progressive Duchenne muscular dystrophy.[6] Although no hyperthermia developed with exposure to 2 general anesthetics, the possibility of malignant hyperthermia still exists. Normal blood lactic acid levels[7] and muscle phosphorylase "b" eliminate McArdle's type V glycogen storage disease. Elevations of serum triglycerides have been associated with the newly described[8] abnormality of fat metabolism in which the enzyme carnitine palmityl transferase is virtually absent from skeletal muscle.

The diagnosis of familial nonprogressive muscular dystrophy was made by neurologic consultation based on abnormalities of EMG, serum CPK in the family, and lack of progressive muscular findings.

Studies by Tammisto and Airaksinen[9,10] have shown that it is possible to induce mild amounts of myoglobinuria in children by the use of 4 intermittent boluses of succinylcholine when given with halothane general anesthesia. They have also indicated that a preinduction dose of curare is protective.[10,11] More recently, Ryan's group,[12] with the aid of a sensitive immune precipitin technic, was able to detect serum myoglobin in the range of 5 to 85 mcg/ml in 40 percent of

TABLE

Results of Clinical Laboratory Tests in 13-Year-Old Boy

Normal limits	Operative day	1st postoperative day	2nd postoperative day	3rd postoperative day	4 months postoperative	1 year postoperative
CPK,* 5-50 μu/ml	110,000	148,000	70,000	30,000	1300	844
SGOT, 7-40 μu/ml	3000	—	300	2490	162	—
LDH, 100-225 μu/ml	4900	—	600	1990	425	—
K^+, 3.5-5 mEq/L	4.1					

*Isoenzyme type III, characteristic of skeletal muscle.

children under general anesthesia following a single 1 mg/kg IV bolus of succinylcholine. This method was so sensitive that, of 16 patients with detectable myoglobinemia, 6 had completely cleared their serum 45 minutes later. Thus, it would appear possible to induce mild amounts of myoglobinuria with multiple doses of succinylcholine in children receiving general anesthesia.

In contrast to these series, Bennike and Jarnum[3] reported an adult patient who was given a single IV bolus of 100 mg of succinylcholine under general anesthesia and later developed massive myoglobinuria with resultant acute renal failure. This patient's serum CPK returned to normal 10 days postoperatively and remained normal. No ischemic exercise test or muscle assay of phosphorylase was reported; however, Bennike felt that the patient had some preexisting muscle disease, possibly McArdle's disease, on the basis of a strong history of intermittent painful swelling of the thighs.

The present case of massive myoglobinuria in a child receiving halothane anesthesia and 2 IV doses of succinylcholine is unusual in that the patient was pretreated with curare and that the proband and family members were found to have persistent elevations of serum CPK. Under normal circumstances, a patient with this form of hereditary muscle disease would not be detected by even the most detailed preoperative history and physical examination. For this reason, a new short-acting, nondepolarizing relaxant drug would be a useful alternative agent, particularly in children.

Since this case documents interaction of a genetic muscle disease with the popular agents, succinylcholine and halothane, any patient with known myopathy or known to have abnormal elevations of type III serum CPK should receive this combination of drugs with caution. Intubation of these patients may be safer without relaxant drugs, or, if relaxants are necessary, with carefully administered nondepolarizing relaxants.

REFERENCES

1. Rowland LP, Penn AS: Myoglobinuria. Med Clin North Am 56:1233-1256, 1972

2. McLaren CAB: Myoglobinuria following the use of suxamethonium chloride. Br J Anaesth 40: 901-902, 1968

3. Bennike KA, Jarnum S: Myoglobinuria with acute renal failure, possibly induced by suxamethonium. A case report. Br J Anaesth 36:730-736, 1964

4. Fisher EH, Krebs EG: Muscle phosphorylase b. Methods Enzymol 5:369-373, 1962

5. Rowland LP, Fahn S, Schotland DL: McArdle's disease. Arch Neurol 9:325-342, 1963

6. Walton JN: Disorders of Voluntary Muscle. Boston, Little, Brown and Company, 1964, pp 389-398

7. McArdle B: Myopathy due to a defect in muscle glycogen breakdown. Clin Sci 10:13-33, 1951

8. Bank WJ, DiMauro S, Bonilla E, et al: A disorder of muscle lipid metabolism and myoglobinuria. N Engl J Med 292:443-449, 1975

9. Tammisto T, Airaksinen M: Increase of creatine kinase activity in serum as sign of muscular injury caused by intermittently administered suxamethonium during halothane anaesthesia. Br J Anaesth 38:510-515, 1966

10. Airaksinen M, Tammisto T: Myoglobinuria after intermittent administration of succinylcholine during halothane anesthesia. Clin Pharmacol Ther 7:583-587, 1966

11. Tammisto T, Leikkonen P, Airaksinen M: The inhibitory effect of d-tubocurarine on the increase of serum creatine kinase activity produced by intermittent suxamethonium administration during halothane anaesthesia. Acta Anaesthesiol Scand 11:333-340, 1967

12. Ryan JF, Kagen LJ, Hyman AI: Myoglobinemia after a single dose of succinylcholine. N Engl J Med 285:824-827, 1971

The Effects of Heparin on Recovery from Ischemic Brain Injuries in Cats

EDWARD H. STULLKEN, JR., MD*
MARTIN D. SOKOLL, MD†
Iowa City, Iowa‡

Since ischemic anoxia in experimental animals has been reported to produce areas of cerebral postocclusive nonperfusion, the authors studied the effect of heparin on recovery from tourniquet-produced cerebrovascular injury in 41 barbiturate-anesthetized, ventilated cats ($Paco_2$ 30 ± 2.5 torr). Twenty-four control animals were subjected to 2-to-12-minute ischemic injuries without further treatment. Seven experimental animals were given heparin (1000 u/kg) 1 minute before 4-to-7-minute ischemic injuries, while 10 animals received heparin (1000 u/kg) immediately after 4-to-7-minute injuries. All animals were monitored with continuous arterial and intracranial pressure (ICP) recordings, EEG, and evoked cortical responses. Ischemia and evoked-response recovery times were linearly related in all groups ($r = 0.998$ control, $r = 0.936$ heparin preinjury, $r = 0.951$ heparin postinjury). Regression-line slope comparison indicated shorter evoked response and EEG recovery times in the heparin-treated groups than in the control group. Heparin administration did not effect elevations of ICP seen 6 and 12 hours postinjury in control versus experimental groups. In cats with injuries lasting 5 minutes or more, all control animals were decerebrate and apneic, while 5/12 heparin-treated animals had lesser neurologic deficits.

THOUGH some studies suggest that the brain is uniquely sensitive to hypoxic injury because of low anaerobic substrate levels,[1] this view is not universally held.[2] Other studies of the effects of total cerebral ischemia have identified areas of postocclusive nonperfusion ("no-reflow" phenomenon).[3-11] Langfitt[12] suggests 2 possibilities: intravascular sludging and red cell aggregation in small vessels during ischemic anoxia, or endothelial and periglial cell swelling with collapse of the cerebral capillary bed, both resulting in subsequent hindrance of reflow.

From direct observations of cerebral microvasculature in dogs during and after induced cardiac arrest, Hekmatpanah[13] believes that greater emphasis should be placed on intravascular obstruction by sludged red blood cells and thrombin microemboli as the etiologic agent in anoxic cerebrovascular (CV) injury. However, Cantu and Ames[8] have shown that increasing jugular venous osmolality with systemic hypertonic mannitol and glucose solutions prior to the ischemic anoxic insult decreases subsequent CV obstruction. Their data would indicate endothelial and periglial cell edema to be the cause of the obstruction.

More recently, Levy's group[14] presented convincing evidence that the no-reflow phenomenon may not occur at all if cerebral perfusion is maintained in the postischemic period. These and other authors[15] relate failure to recover neuronal function after ischemia to primary neuronal injury resulting in massive increases in perivascular potassium concentration released during the

*Resident.
†Professor.
‡Department of Anesthesia, University of Iowa School of Medicine, Iowa City, Iowa 52242.
This study was supported in part by the Department of Anesthesia Trust Fund.
Paper received: 6/13/75
Accepted for publication: 1/30/76

ischemic period. Many authors[8,13,16] agree that systemic hypertension after ischemic anoxic injury improves recovery.

Sodium heparin, when used in doses larger than those employed in anticoagulant therapy, is known to have anti-inflammatory and antihistaminic properties.[17-20] Saliba and coworkers[21] found parenteral heparin useful in reducing tissue necrosis and loss in burned patients. On the basis of these reports, we studied the effects of parenteral heparin on recovery from ischemic anoxic brain injuries in cats.

METHODS AND MATERIALS

Forty-one adult cats were divided into 3 groups; (I) 24 control animals given 2-to-12-minute ischemic anoxic injuries without therapy; (II) 7 experimental animals given heparin (1000 u/kg) 1 minute before ischemic anoxic injuries lasting 4 to 7 minutes; (III) 10 experimental animals given heparin (1000 u/kg) immediately after injuries of 4 to 7 minutes duration.

The cats were anesthetized with intraperitoneal sodium pentobarbital (25 mg/kg), intubated, and ventilated with a Harvard pump and room air to maintain a $Paco_2$ of 30 ± 2.5 torr. Esophageal temperatures were maintained at 36 ± 0.5° C. Arterial and venous cannulae were inserted in femoral vessels and a Richmond ICP bolt was placed in the right parietal subarachnoid space.[22,23] Continuous arterial and intracranial pressures were recorded on a Beckman R 411 Dynograph® via Statham P23Db transducers and 5 percent dextrose in water was infused through the venous cannula at 5 ml/kg/hr.

A shielded silver-silver chloride electrode was inserted through the left frontal sinus onto the surface of the frontal cortex and sealed in place with Eastman 910 adhesive. Continuous unipolar EEG activity and cortical evoked responses to electrical stimulation of the right forepaw (10 v, 1 msec, 0.33 Hz) were recorded from the silver-silver chloride electrode with reference to an indifferent ear electrode. The EEG and evoked cortical responses were recorded on a Tektronix® 564 B storage oscilloscope after passage through a preamplifier and 60 Hz filter.

Ischemic anoxic injuries were produced by inflating a pneumatic cuff around the neck to 1200 torr. The adequacy of this method of interrupting cerebral blood flow was tested by injecting fluorescein dye IV in 5 cats immediately after cuff inflation, and, in another 5 cats, immediately after bilateral vertebral and carotid artery clamping. The appearance time for trace amounts of dye on the cerebral cortex was 2.5 ± 0.2 minutes postinjection in both groups.

Neither of these recognized methods produce complete cerebral ischemia. We could demonstrate no significant difference between the 2 methods and chose the less invasive. Minimal flow probably continued through the anterior spinal artery. Hossman and Kleihues[7] indicated that this remaining flow is not significant and may indeed interfere with recovery.

An evoked cortical somatic response was chosen as a sensitive monitor of multineural ischemic anoxic injury and subsequent recovery.[7] The preinjury appearance of the evoked response, its disappearance time after cuff inflation, and its reappearance time after cuff release were noted in all animals. The disappearance time of the evoked response was taken as the point of complete loss of wave-form. A response 10 percent of control amplitude was chosen as the reappearance point. Disappearance and reappearance times for EEG activity were also noted. Evoked response recovery times after cuff release were plotted as a function of cuff inflation time. Regression lines and correlation coefficients were calculated. Differences in line slopes were subjected to *Z* analysis.*

All animals were then observed for 24 hours. Mean arterial pressures (MAP) were maintained at 100 to 120 torr with norepinephrine during observation period. The development and intensity of cerebral edema was evaluated by continuous ICP recordings. The neurologic state of all cats was examined 24 hours postinjury.

RESULTS

EEG and evoked-response tracings were similar in all animals before cuff inflation (fig 1). Disappearance times of EEG and evoked response after cuff inflation did not vary between control or experimental groups. All animals responded to cuff inflation with tachycardia, hypertension, and arrhythmias. After cuff release, 11/24 control animals and 8/17 experimental animals required intermittent norepinephrine administration to maintain MAP greater than 100 torr (fig 2).

*Z analysis: a test that compares regression-line slopes for significance of variance. Steel and Torrie: Principles and Procedures of Statistics. New York, McGraw Hill & Company, 1960, pp 188-191.

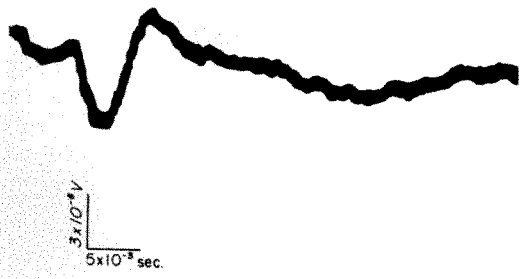


FIG 1. Example of control somatic cortical evoked response tracing.

The duration of ischemic injury was linearly related to evoked-response recovery times in all groups (fig 3). Regression lines for the 2 experimental groups (B, C, fig 3) differed significantly from that of the control group (A, fig 3). The Z factor between control and heparin preinjury regression-line slopes was 1.76 ($p<0.032$). Regression-line slopes for the 2 experimental groups were not significantly different ($Z=0.239$) ($p>0.05$).

Postinjury EEG recovery times were not as well related to the duration of ischemia as were those for evoked response, EEG activity consistently appearing after the evoked response. The difference between these recovery times was directly proportional to the duration of cuff inflation. Correlation coefficients for ischemia versus EEG recovery times were 0.791 for control animals, 0.818 for heparin preinjury treated animals, and 0.786 for heparin postinjury treated animals.

Control ICP was 6.1 ± 3.1 torr (SD) for all 41 cats studied. During cuff inflation, ICP decreased 2.9 ± 1.6 torr for all cats.

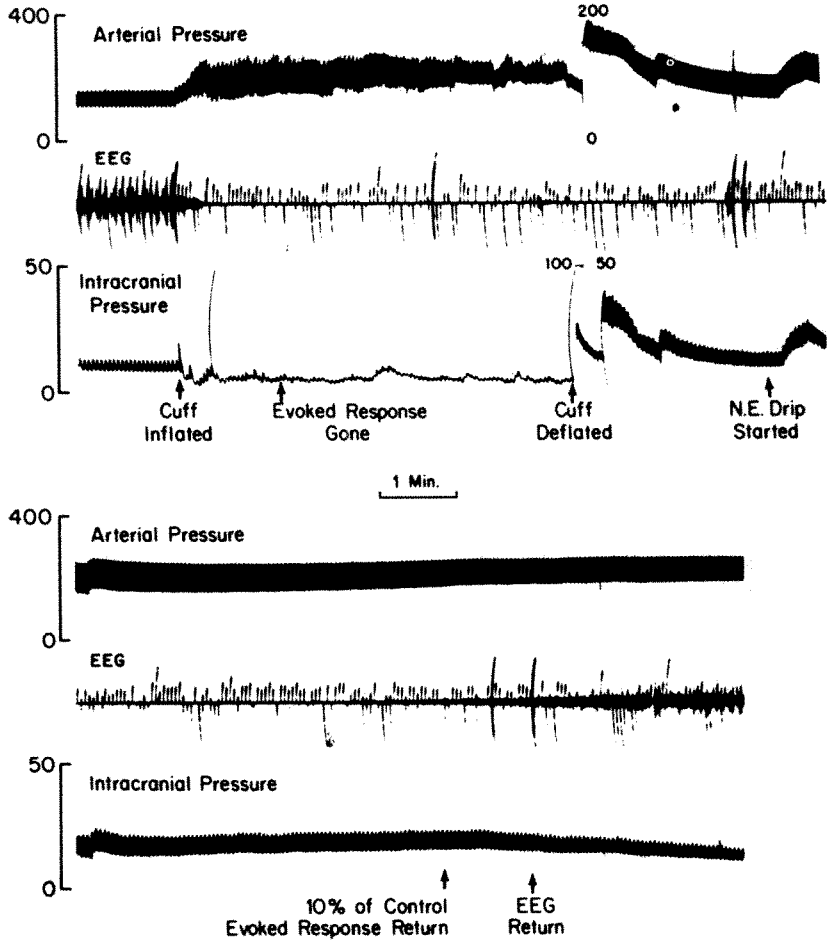


FIG 2. Effect of cuff inflation and release on arterial pressure (top line), EEG (middle lines), and ICP (bottom line). The figure is read from left to right and the 3 tracings are continued in the bottom half of the figure. The 0.33 Hz spikes in the EEG tracings are artifacts.

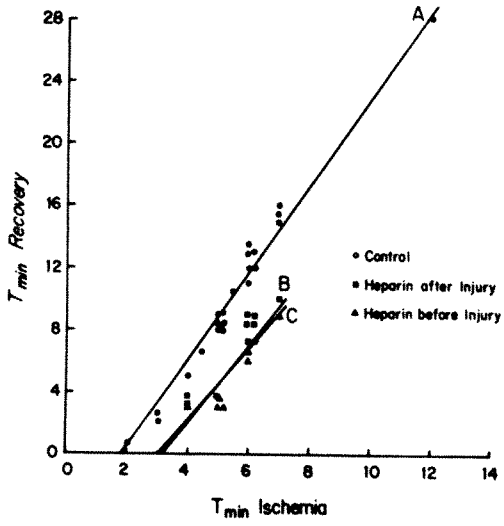


FIG 3. A. Regression line for control animals. B. Regression line for experimental animals given heparin before injury. C. Regression line for experimental animals given heparin after injury.

Immediately after cuff release, ICP increased to 32.3 ± 7.9 torr and then gradually returned to near control levels within 30 minutes (fig 2). A later sustained increase in ICP was noted beginning 3 to 4 hours postinjury. The degree of this late increase was variable for all cats studied and not related, at a confidence level of $p<0.05$, to either the duration of ischemic injury or the administration of heparin.

The neurologic status of cats 24 hours postinjury was dependent both on the duration of injury and the administration of heparin. Ten cats received ischemic injuries of less than 5 minutes duration. Five control cats manifested variable neurologic deficits 24 hours after injury. One was apneic and decerebrate while 4 were severely ataxic. Five of the 17 cats given heparin either immediately before or after injury were less severely impaired after 24 hours; 2 appeared neurologically intact while 3 manifested variable degrees of ataxia.

The 19 control cats given ischemic injuries of 5 minutes or more were all apneic and decerebrate after 24 hours. The 12 experimental cats that received ischemic injuries of 5 minutes or more manifested variable neurologic findings after 24 hours; 7 were apneic and decerebrate while 5 were breathing spontaneously and reacted to stimuli. Of these latter, 3 were ataxic and 2 were quadriparetic.

DISCUSSION

This study shows that heparin modifies the response of cats to ischemic anoxic CV injury. Regression-line slope comparison of control animals with heparin-treated animals indicated a more rapid return of evoked response activity in the heparin-treated groups after ischemic injuries of 4 to 7 minutes duration. There was no significant difference in recovery, whether heparin was administered before or after injury.

Fischer and Ames,[16] studying longer anoxic injuries in rabbits, did not find heparin beneficial for postischemic recirculation. This discrepancy may be due to heparin inactivation at low pH levels. Cats in our study had a blood pH of 7.45 ± 0.05 from controlled mild hyperventilation before ischemic injury. They sustained injuries of shorter duration than animals in Fischer's study and, therefore, probably had lesser degrees of intracerebral acidosis immediately after injury. Systemic pH in our cats was not significantly different before than after injury.

Many authors[3,8,10] state that microvascular obstruction from thrombotic debris is not a major factor in ischemic injuries of less than 5 minutes duration, yet our results reveal a beneficial effect of heparin on recovery from 4-to-7-minute ischemic anoxic injuries. This would indicate that heparin may reduce endothelial and periglial cell edema as well as prevent thrombotic accumulation in cerebral capillary beds.

The high correlation coefficients demonstrated for evoked-response regression lines in all 3 groups of cats support the assumption that evoked somatic cortical responses are sensitive reproducible indicators of recovery from ischemic injury. Regression lines for EEG recovery had lower correlation coefficients. The nature of the evoked-response recovery lines also indicates that the cuff-inflation method of causing ischemic anoxic injury is reproducible. Dye appearance on the cerebral cortex after both methods of occlusion indicates that neither method interrupts collateral flow (most likely through the anterior spinal artery).

Comparison of neurologic findings for control and experimental animals 24 hours postinjury also revealed heparin-induced differences. With injuries of 5 or more minutes duration, control animals were all decerebrate and apneic, while 5/12 heparin-treated animals had lesser neurologic impairment.

Our results failed to demonstrate parallel differences in postinjury intracranial hypertension between control and experimental groups. Failure to demonstrate this expected correlation might be attributed either to inaccuracies in long-term pressure recordings from the Richmond bolt in thin cat skulls or to the small size of the experimental-animal sample.

This study has, however, demonstrated the need for further detailed investigation of heparin use in decreasing the degree of CV injury after ischemic anoxia. It also describes a relatively simple and reproducible experimental design for studying drug effect on CV ischemic injury.

ACKNOWLEDGMENT

The authors wish to thank Mr. L. R. Davies for his expert technical assistance.

REFERENCES

1. Reichelt KL: The chemical basis for the intolerance of the brain to anoxia. Acta Anaesthesiol Scand Suppl 29:35-46, 1968

2. Hossman KA, Sato K: Recovery of neuronal function after prolonged cerebral ischemia. Science 168: 375-376, 1970

3. Fischer EG: Impaired perfusion following cerebrovascular stasis—a review. Arch Neurol 29: 361-366, 1973

4. Ames A III, Gurian BS: Effects of glucose and oxygen deprivation on function of isolated mammalian retina. J Neurophysiol 26:617-634, 1963

5. Neely WA, Youmans JR: Anoxia of canine brain without damage. JAMA 183:1085-1087, 1963

6. Ames A III, Wright RL, Kowada J: Cerebral ischemia. II. The no-reflow phenomenon. Am J Pathol 52:437-453, 1968

7. Hossman KA, Kleihues P: Reversibility of ischemic brain damage. Arch Neurol 29:375-384, 1973

8. Cantu RC, Ames A III: Experimental prevention of cerebral vasculature obstruction produced by ischemia. J Neurosurg 30:50-54, 1968

9. Chiang J, Kowada J, Ames A III: Cerebral ischemia. III. Vascular changes. Am J Pathol 52: 455-476, 1968

10. Kowada M, Ames A III, Magno G: Cerebral ischemia. I. An improved experimental method for study: cardiovascular effects and demonstration of an early vascular lesion in the rabbit. J Neurosurg 28:150-157, 1968

11. Siesjo BK: Metabolism and flow in the hypoxic brain. Eur Neurol 6:43-48, 1971-72

12. Langfitt TW: Cerebral circulation and metabolism. Summary of international symposium, June 6-10, 1973. J Neurosurg 40:561-576, 1974

13. Hekmatpanah J: Cerebral blood flow dynamics in hypotension and cardiac arrest. Neurology 23:174-180, 1973

14. Levy DE, Brierley JB, Silverman DG, et al: Brief hypoxia-ischemia initally damages cerebral neurons. Arch Neurol 32:450-456, 1975

15. Wade JG, Amtorp O, Sorensen SC: No-flow state following cerebral ischemia. Arch Neurol 32: 381-384, 1975

16. Fischer EG, Ames A III: Studies on mechanical impairment of cerebral circulation following ischemia: effect of hemodilution and perfusion pressure. Stroke 3:538-542, 1972

17. Dolowitz DA, Dougherty TF: The use of heparin as an anti-inflammatory agent. Laryngoscope 70:873-874, 1960

18. Dougherty TF, Dolowitz DA: Physiologic aspects of heparin not related to blood clotting. Am J Cardiol 14:18-24, 1964

19. Boyle JP, Smart RH, Shirley JK: Heparin in the treatment of chronic obstructive bronchopulmonary disease. Am J Cardiol 14:25-28, 1964

20. Griffith GC, Boggs RP: Clinical use of heparin. Am J Cardiol 14:39-46, 1964

21. Saliba MJ Jr, Dempsey WC, Kruggel JL: Large burns in humans. Treatment with heparin. JAMA 225:261-269, 1973

22. Vries JK, Becker DP, Young HF: A subarachnoid screw for monitoring intracranial pressure. J Neurosurg 39:416-419, 1973

23. Stullken EH Jr, Sokoll MD: Intracranial pressure during hypotension and subsequent vasopressor therapy in anesthetized cats. Anesthesiology 42:425-431, 1975

Change in Pulmonary Venous Admixture With Varying Inspired Oxygen

MICHAEL E. DOUGLAS, MAJOR, USAF (MC)*
JOHN B. DOWNS, MD†
FRANCIS J. DANNEMILLER, COLONEL, USAF (MC)‡
MICHAEL R. HODGES§
EDWIN S. MUNSON, MD‖

Pulmonary venous admixture ($\dot{Q}sp/\dot{Q}t$) was analyzed as a function of fractional concentration of inspired O_2 (F_{IO_2}) in 30 patients who required postoperative mechanical ventilation. Pulmonary and radial artery blood-gas tensions and pH were measured and $\dot{Q}sp/\dot{Q}t$ was calculated with F_{IO_2} ranging from 0.21 to 1. In all patients, $\dot{Q}sp/\dot{Q}t$ decreased when F_{IO_2} was increased from 0.21 to 0.4 and then stabilized to an F_{IO_2} of approximately 0.6. As the F_{IO_2} was increased to 1, $\dot{Q}sp/\dot{Q}t$ increased. Since the inhalation of gas mixture with $F_{IO_2} \geq 0.6$ increased right-to-left intrapulmonary shunting of blood, we recommend respiratory function be evaluated during inhalation of a clinically useful concentration of O_2 rather than at an F_{IO_2} of 1.

PULMONARY venous admixture ($\dot{Q}sp/\dot{Q}t$) may result from intrapulmonary arteriovenous shunting of blood, or from shunt-like effects produced by decreased O_2 diffusion through the alveolar capillary membrane, and perfusion of lung units with small but finite ventilation/perfusion ratios.[1] Determination of $\dot{Q}sp/\dot{Q}t$ by the equation derived from a 2-compartment model gives an estimation of the right-to-left intrapulmonary shunting of blood that would have to exist to explain the observed differences between pulmonary end-capillary and systemic Pao_2. However, the various causes of $\dot{Q}sp/\dot{Q}t$ cannot be distinguished by such a 2-compartment model.[2]

Pure O_2 inhalation will minimize both diffusion abnormalities and the effect of $\dot{Q}sp/\dot{Q}t$ on lung units with low $\dot{V}_A/\dot{Q}$.[3] However, recent evidence[4,5] suggests that overall $\dot{Q}sp/\dot{Q}t$ may not be minimized, and that intrapulmonary shunt may actually increase, even with short periods of O_2 inhalation. Our study was performed to quantitate the effect of elevated F_{IO_2} on $\dot{Q}sp/\dot{Q}t$ in patients requiring continuous mechanical respiratory support.

METHODS

Data were obtained from 30 surgical patients admitted to the intensive care unit during a 6-month period. All patients either had been unable to maintain arterial pH (pHa) ≥ 7.35 because of respiratory depression or had elevated $\dot{Q}sp/\dot{Q}t$. Pulmonary and radial artery catheters were inserted percutaneously. Each patient was intubated

*Chief, Recovery Room/Intensive Care Service, Wilford Hall USAF Medical Center, Lackland AFB, Texas.

†Assistant Professor, Department of Anesthesiology and Surgery, University of Florida College of Medicine and Veterans Administration Hospital, Gainesville, Florida.

‡Chief, Department of Anesthesiology, Wilford Hall AFB.

§Research Technician, Department of Anesthesiology, University of Utah College of Medicine, Salt Lake City, Utah.

‖Professor of Anesthesiology, University of Florida College of Medicine.

Reprint requests to Dr. Downs, Department of Anesthesiology, University of Florida College of Medicine, Box J-254, J. Hillis Miller Health Center, Gainesville, Florida 32610.

Paper received: 7/23/75
Accepted for publication: 2/2/76
This study was a part of Veterans Administration Project #573-1917-01.

orotracheally and mechanical ventilatory support was provided with an intermittent mandatory ventilation volume-cycled ventilator (J. H. Emerson Company). A mandatory tidal volume of 12 ml/kg was delivered with sufficient frequency to maintain a pHa $\geq$ 7.35. A precalibrated, high-flow, air-O_2 blender (bird Corporation) with verified accuracy of $\pm$ 1% of the indicated F_{IO_2} provided a continuously heated and humidified gas flow (20 to 30 L/min) which allowed patients to breathe spontaneously between mechanical breaths. A threshold-resistor valve (J. H. Emerson Company) provided PEEP when indicated.

No patient showed evidence of chronic obstructive lung disease and all had stable vital signs and a hemoglobin (hgb) concentration $\geq$ 11 gm/100 ml. In all patients, P_{aO_2} values were $\geq$50 torr (F_{IO_2} = 0.21) and the pHa was between 7.35 and 7.55. Proper orotracheal tube placement was confirmed by chest roentgenogram. Clinical data on individual patients are shown in table 1.

Each patient received an F_{IO_2} of 0.21 for 30 minutes before heparinized pulmonary and radial arterial blood samples were collected anaerobically. Blood-gas tension and pH were determined with standard electrode technics (Instrumentation Laboratories). F_{IO_2} was increased to 0.3 for 15 minutes and blood samples again were collected. This sequence was repeated at 15-minute intervals using F_{IO_2}'s of 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, and 1.

$\dot{Q}sp/\dot{Q}t$ was calculated at each F_{IO_2} using the equation:

$$\dot{Q}sp/\dot{Q}t = \frac{C\acute{c}o_2 - Cao_2}{C\acute{c}o_2 - C\bar{v}o_2}$$

where Cao_2 = 1.34 (hgb) (Sao_2) + 0.0031 Pao_2; $C\bar{v}o_2$ = 1.34 (hgb) ($S\bar{v}o_2$) + 0.0031 $P\bar{v}o_2$; $C\acute{c}o_2$ = 1.34 (hgb) ($S\acute{c}o_2$) + 0.0031 [($P_B - P_{H_2O}$) $F_{IO_2} - P_{ACO_2}$]; Sao_2, $S\bar{v}o_2$ and $S\acute{c}o_2$ are O_2 saturations of arterial, pulmonary artery, and pulmonary end-capillary hgb, respectively, and P_B is barometric pressure; the respiratory quotient was assumed equal to 1; 1.34 = O_2 capacity of hgb in ml O_2/gm hgb,[2] and 0.0031 = O_2 solubility coefficient in O_2 ml/torr. O_2 saturation was calculated by the method described by Severinghaus.[6] $P\acute{c}o_2$ was assumed equal to estimated P_{AO_2}.[2]

In 5 randomly selected patients, heart rate, mean pulmonary artery pressure, mean systemic blood pressure, pulmonary artery occlusion pressure, and cardiac output determined by thermodilution technic[7] were measured at each F_{IO_2}. An *in vivo* O_2 electrode (International Biophysics Corporation) was inserted in the radial artery so that Pao_2 response to changing F_{IO_2} could be measured continuously. To assess the possible influence of mechanical ventilation, PEEP, and cardiac output on the relationship between F_{IO_2} and $\dot{Q}sp/\dot{Q}t$, patients retrospectively were divided into subgroups as follows: group A (8 patients) had an IMV rate $\geq$ 6/min; group B (11 patients) received PEEP $\geq$ 10 torr; group C (19 patients) received PEEP $\geq$ 4 torr; group D (7 patients) had a $P\bar{v}o_2 \leq$ 30 torr (F_{IO_2} = 0.21); group E (9 patients) had a $P\bar{v}o_2 \leq$ 38 torr (F_{IO_2} = 0.7); group F (10 patients) had $P\bar{v}o_2 \leq$ 40 torr (F_{IO_2} = 1). Data were examined statistically using an analysis of variance (ANOV) and the paired 2-tailed Student's *t*-test when ANOV indicated significant differences.

SYMBOLS*

Cao_2: arterial blood O_2 content (volumes percent)

$C\acute{c}o_2$: pulmonary end-capillary blood O_2 content (volumes percent)

$C\bar{v}o_2$: pulmonary artery (mixed venous) blood O_2 content (volumes percent)

F_{IO_2}: fractional concentration of inspired O_2

P_{ACO_2}: alveolar CO_2 tension (torr)

P_{AN_2}: alveolar N_2 tension (torr)

P_{AO_2}: alveolar O_2 tension (torr)

$P_{(A\text{-}a)O_2}$: alveolar-arterial O_2 tension difference

Pao_2: arterial blocd O_2 tension (torr)

$P\acute{c}o_2$: pulmonary end-capillary blood O_2 tension (torr)

PEEP: positive end-expiratory pressure (torr)

$P\bar{v}o_2$: pulmonary artery (mixed venous) blood O_2 tension (torr)

$\dot{Q}sp/\dot{Q}t$: fraction of pulmonary physiologic shunt flow (venous admixture)

$\dot{Q}san/\dot{Q}t$: a special case of $\dot{Q}sp/\dot{Q}t$ when F_{IO_2} = 1

$\dot{V}_A/\dot{Q}$: ratio of alveolar ventilation to pulmonary perfusion

*American College of Chest Physicians, American Thoracic Society, Pulmonary Terms and Symbols: A Report of the ACCP-ATS Joint Committee on Pulmonary Nomenclature. Chest 67:583-593, 1975 (supplemented).

TABLE 1

Patient Clinical Data

Patient number	Age, yr	Sex	Diagnosis or operation	IMV rate, cycles/min	PEEP, torr	$\dot{Q}sp/\dot{Q}t$, $F_{IO_2}=0.4$
1	41	M	Coronary artery-saphenous vein graft (CASVG)	0	10	0.15
2	62	M	Gram-negative septicemia	8	0	0.21
3	24	F	Aspiration pneumonitis	2	6	0.12
4	58	M	Gram-negative septicemia	4	6	0.21
5	40	F	CASVG	4	0	0.06
6	55	M	CASVG	7	0	0.09
7	61	M	Gram-negative septicemia	4	20	0.18
8	54	M	Small-bowel obstruction	2	10	0.11
9	43	F	Aspiration pneumonitis; hemorrhagic shock	3	20	0.16
10	58	F	Mitral valve commissurotomy	4	0	0.14
11	49	M	Left ventricular aneurysmectomy	6	0	0.22
12	53	M	CASVG	6	10	0.05
13	28	M	CASVG	2	0	0.15
14	20	M	Exploratory laparotomy	2	8	0.16
15	53	M	CASVG	3	0	0.06
16	41	F	Adrenalectomy	4	0	0.18
17	38	M	CASVG	8	20	0.18
18	15	F	Repair atrial septal defect	10	0	0.20
19	42	M	Aortic valve replacement	1	4	0.15
20	19	M	Lung contusion	3	20	0.15
21	56	M	Aortic bifemoral graft placement	1	5	0.05
22	28	F	Aortic valve replacement	1	0	0.09
23	52	F	Hysterectomy and congestive heart failure	6	15	0.14
24	50	M	CASVG	12	15	0.04
25	20	F	Septic abortion	4	10	0.06
26	55	M	CASVG	5	4	0.09
27	53	M	CASVG	2	10	0.16
28	35	F	Abdominal exploration	0	8	0.13
29	45	M	Mitral valve replacement	5	0	0.14
30	55	F	CASVG	1	5	0.14

RESULTS

When plotted as a function of F_{IO_2}, $\dot{Q}sp/\dot{Q}t$ formed a convex curve with a minimum value occurring between F_{IO_2} = 0.4 and 0.7 for each patient (figure). As F_{IO_2} was raised from 0.21 to 0.4, $\dot{Q}sp/\dot{Q}t$ decreased and then remained unchanged as F_{IO_2} was raised to 0.7. $\dot{Q}sp/\dot{Q}t$ increased as F_{IO_2} was raised to 1, but was less than when F_{IO_2} was 0.21 ($p<0.001$).

Patients in subgroups A, B, C, D, E, and F showed no significant change in trends of mean $\dot{Q}sp/\dot{Q}t$ when data from subgroups were compared with those of all other patients. *In vivo* Pa_{O_2} recordings revealed that 90% of the change in Pa_{O_2} occurred within 5 minutes of increasing F_{IO_2} by 0.1 and within 7 minutes of increasing F_{IO_2} by 0.79. Complete equilibration was reached by 15 minutes when F_{IO_2} was increased directly from 0.21 to 1. There were no differences in cardiac output, heart rate, mean pulmonary artery pressure, mean systemic blood pressure, pulmonary artery wedge pressure or $Ca\text{-}\bar{v}O_2$ as F_{IO_2} was increased in 5 patients (table 2).

DISCUSSION

Adequate pulmonary gas exchange is essential to the successful management of critically ill patients. Various methods have been advocated to evaluate pulmonary function and effectiveness of therapy. Pa_{O_2} and $P(A\text{-}a)O_2$ vary with F_{IO_2} and may be influenced significantly by O_2 consumption and cardiac output.[8,9] Therefore, estimating $\dot{Q}sp/\dot{Q}t$ with these measurements alone may be misleading.[9] When $\dot{Q}sp/\dot{Q}t$ is calculated directly from Ca_{O_2} and $C\bar{v}O_2$ measurements and calculated $C\acute{c}O_2$,[10] one can determine whether $\dot{Q}sp/\dot{Q}t$, cardiac output, or O_2 consumption is primarily responsible for arterial hypoxemia. It has been thought that establishing an F_{IO_2} of 1 will insure that

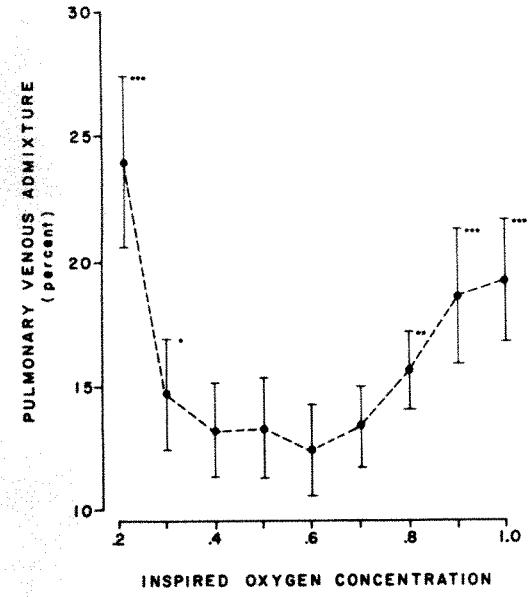


FIGURE. Calculated mean pulmonary venous admixture as a function of inspired O_2 concentration. Values represent mean ± 2 SE of 30 observations. (Asterisks indicate significant difference from value observed at F_{IO_2} = 0.6; *$p<0.05$, **$p<0.01$, ***$p<0.001$.)

calculated $\dot{Q}sp/\dot{Q}t$ is secondary only to direct intrapulmonary right-to-left shunting of blood[8] and will not produce detrimental side effects if confined to brief periods of exposure. For this reason, several authors have recommended that pulmonary gas exchange be evaluated during inhalation of 100% O_2.[11-14]

The significant decrease in $\dot{Q}sp/\dot{Q}t$ which occurred as F_{IO_2} was increased to 0.4 may have been the result of 2 factors. Interstitial pulmonary edema may have created a relative barrier to O_2 diffusion across the alveolar-capillary membrane. Additionally, areas with low $\dot{V}_A/\dot{Q}$ ratios will cause P_{AO_2} and $C\acute{c}O_2$ to be lower than estimated and, therefore, increase $\dot{Q}sp/\dot{Q}t$ during inhalation of room air. With increasing F_{IO_2}, the elevated P_{O_2} gradient across the alveolar-capillary junction may promote better O_2 diffusion. Increased F_{IO_2} also will increase P_{AO_2} and decrease P_{AN_2} in poorly ventilated lung units. In both instances, Ca_{O_2} will increase, lowering calculated $\dot{Q}sp/\dot{Q}t$. Since no significant change occurred in $\dot{Q}sp/\dot{Q}t$ as F_{IO_2} was increased from 0.4 to 0.6, effects of diffusion abnormalities and areas with low $\dot{V}_A/\dot{Q}$ on $\dot{Q}sp/\dot{Q}t$ may have been minimized.

TABLE 2

Cardiopulmonary Responses Measured at Various F_{IO_2} Values (Mean ± SD)

	(n)	F_{IO_2} 0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Cardiac output, L/min	(5)	5.1 ±1.5	5.4 ±1.5	5.4 ±1.5	5.6 ±1.9	5.2 ±1.2	5.7 ±1.6	5.5 ±1.7	5.5 ±1.6	5.7 ±1.6
Heart rate, beats/min	(5)	113 ±5	113 ±5	110 ±8	110 ±8	111 ±3	115 ±4	111 ±3	111 ±2	111 ±2
Pulmonary artery pressure, torr	(5)	19.3 ±9.1	19.0 ±10.8	19.0 ±10.8	18.5 ±9.3	18.5 ±10.0	17.8 ±9.3	18.3 ±10.2	18.5 ±10.0	17.8 ±10.7
Pulmonary artery occlusion pressure, torr	(5)	12.8 ±10.4	12.3 ±10.6	13.0 ±10.0	13.0 ±10.0	13.0 ±10.1	13.5 ±9.9	13.5 ±9.9	13.5 ±9.9	12.8 ±10.3
Systemic arterial pressure, torr	(5)	101 ±6	104 ±8	106 ±11	106 ±11	110 ±12	110 ±12	103 ±10	103 ±10	103 ±10
Arteriovenous O_2 content difference, ml/100 ml blood	(30)	5.0 ±1.3	5.1 ±1.3	5.1 ±1.3	4.9 ±1.3	4.8 ±1.2	4.5 ±1.2	4.3 ±1.2	4.4 ±1.4	4.4 ±1.5

(n) = number of patients studied.

Several factors may have influenced the increase in $\dot{Q}sp/\dot{Q}t$ when F_{IO_2} was raised from 0.7 to 1. Absorption atelectasis and decreased functional residual capacity (FRC) may occur during inhalation of 100% O_2.[4,15,16] However, decreased FRC has been shown to correlate poorly with $\dot{Q}sp/\dot{Q}t$ in some patients.[17] Therefore, even if absorption atelectasis caused increased $\dot{Q}sp/\dot{Q}t$ at elevated F_{IO_2}, it may not have been the only contributing factor. Ramachandran and Fairley[18] reported that 5% N_2 added to the inhaled gas mixture will prevent absorption atelectasis. One might also expect PEEP to minimize the effects of absorption atelectasis by increasing FRC.[4,17] The $\dot{Q}sp/\dot{Q}t$ of patients in groups B and C who were treated with PEEP increased by the same magnitude as that of the patients who did not receive PEEP. Therefore, increase in $\dot{Q}sp/\dot{Q}t$, particularly F_{IO_2}'s of 0.8 and 0.9 may have been caused by factors other than absorption atelectasis.

West[19] has suggested that there may be a greater increase in $\dot{Q}sp/\dot{Q}t$ in response to increased F_{IO_2} when $P\bar{v}O_2$ is low. In this situation, the increased $P(A\text{-}a)O_2$ gradient would cause a more rapid efflux of O_2 from alveoli to capillary blood. If net gas outflow from alveoli into capillaries exceeds gas inflow from the airways, alveolar collapse could occur. Comparison of the response of $\dot{Q}sp/\dot{Q}t$ to increased F_{IO_2} in patients with low $P\bar{v}O_2$ and in those with elevated $P\bar{v}O_2$ revealed no significant differences. Although $C\bar{v}O_2$ varied widely in our patients, $P\bar{v}O_2$ was relatively constant (range 25 to 53 torr). This suggests that the small differences observed in $P\bar{v}O_2$ of 20 to 30 torr may be insignificant in promoting alveolar collapse with increasing P_{AO_2}.

Hypoxic pulmonary vasoconstriction is thought to occur in areas with low $\dot{V}_A/\dot{Q}$.[20] Alveolar gas in such areas will not equilibrate completely with upper airway gas but will equilibrate with mixed-venous blood. Precapillary pulmonary vasoconstriction normally will shunt blood away from these units to areas with better ventilation, thus improving overall $\dot{V}_A/\dot{Q}$.[21,22] When F_{IO_2} is increased sufficiently, P_{AO_2} will rise, $P\bar{v}O_2$ will increase, and the degree of hypoxic vasoconstriction may decrease. The resulting increase in perfusion to areas with low $\dot{V}_A/\dot{Q}$ could cause $\dot{Q}sp/\dot{Q}t$ to increase. This mechanism may be responsible for the observed increase in $\dot{Q}sp/\dot{Q}t$ in response to elevated cardiac output,[22-24] since increased cardiac output will cause an increase in $C\bar{v}O_2$ and $P\bar{v}O_2$.[25] All our patients responded to increasing F_{IO_2} with an elevated $P\bar{v}O_2$; therefore, the increase in $\dot{Q}sp/\dot{Q}t$ also may have been caused by release of hypoxic pulmonary vasoconstriction.

A 3rd explanation for the increased $\dot{Q}sp/\dot{Q}t$ is extra alveolar intrapulmonary shunting of venous blood. Such anatomic shunting has been shown to occur with chronic obstructive pulmonary disease,[26] and following IV infusion of epinephrine,[27] both with radioactive tracer materials[28,29] and histologically.[30] Nomoto's group[27] has suggested that such shunts may be responsible for hypoxemia in some critically ill patients with respiratory failure.

As has been previously reported,[15] N_2 washout occurred within 15 minutes when F_{IO_2} was raised from 0.21 directly to 1, supporting the contention that P_{AO_2} was stable by 15 minutes when F_{IO_2} was increased by only 0.1. Therefore, a lack of equilibration of pulmonary capillary and alveolar gas tension was an unlikely source of variation in $\dot{Q}sp/\dot{Q}t$. There was no change in cardiac output, heart rate, systemic blood pressure, mean pulmonary artery pressure, or pulmonary artery occlusion pressure as F_{IO_2} was increased. Therefore, changes in $\dot{Q}sp/\dot{Q}t$ could not be explained by variation in overall pulmonary or systemic vascular resistance. Erroneous assumption of a respiratory quotient of 1 could have induced a maximum error of +3% in calculating $\dot{Q}sp/\dot{Q}t$ with $F_{IO_2} = 0.21$, and then only if $P_{aCO_2} \geq 50$ torr, which was not the case in any patient.

Several authors[11,13,14] have advocated therapeutic respiratory maneuvers directed toward minimization of calculated $\dot{Q}san/\dot{Q}t$ which requires $F_{IO_2} = 1$. However, regardless of etiology, $F_{IO_2} \geq 0.7$ caused significant increase in $\dot{Q}san/\dot{Q}t$ in every patient studied. Therefore, treatment based on measurement of $\dot{Q}san/\dot{Q}t$ may be directed at reversing a pathologic condition induced by measurement conditions and not necessarily by the patient's primary pathophysiologic process. For this reason, we recommend that evaluations of patients' respiratory status be conducted with a clinically useful F_{IO_2}, which, in most instances, will range from 0.4 to 0.6 and will minimize calculated $\dot{Q}sp/\dot{Q}t$.

ACKNOWLEDGMENT

The authors thank Ms. Cindy Bunt and

Ms. Barbara Alspaugh for secretarial assistance; Ms. Dianne Kosman for editorial help; George Policello for statistical assistance; Jerome H. Modell, MD, for his support and advice; and the staff of the Surgical Intensive Care Unit for their invaluable aid.

REFERENCES

1. Nunn JF: Applied Respiratory Physiology. Scarborough, Ontario, Butterworths, 1969, chapter 9

2. Laver MB, Seifen A: Measurement of blood oxygen tension in anesthesia. Anesthesiology 26:73-101, 1965

3. Wagner PD, Laravuso RB, Uhl RR, et al: Continuous distribution of ventilation-perfusion ratios in normal subjects breathing air and 100% O_2. J Clin Invest 54:54-68, 1974

4. Suter PM, Fairley HB, Schlobohm RM: The response of lung volume and pulmonary perfusion to short periods of 100% oxygen ventilation in acute respiratory failure. Crit Care Med 2:43-44, 1974

5. McAslan TC, Matjasko-Chiu J, Turney SZ, et al: Influence of inhalation of 100 percent oxygen on intrapulmonary shunt in severely traumatized patients. J Trauma 13:811-821, 1973

6. Severinghaus JW: Blood gas calculator. J Appl Physiol 21:1108-1116, 1966

7. Forrester JS, Ganz W, Diamond G, et al: Thermodilution cardiac output determination with a single flow-directed catheter. Am Heart J 83:306-311, 1972

8. Pontoppidan H, Geffin B, Lowenstein E: Acute respiratory failure in the adult. N Engl J Med 287:690-698, 743-752, 799-806, 1972

9. Mitchell LA, Downs JB, Dannemiller FJ: Extrapulmonary influences on $A\text{-}aDo_2^{1.0}$ following cardiopulmonary bypass. Anesthesiology 43:583-586, 1975

10. Downs JB, Klein EF Jr, Modell JH: The effect of incremental PEEP on Pao_2 in patients with respiratory failure. Anesth Analg 52:210-215, 1973

11. Farhi LE, Rahn H: A theoretical analysis of the alveolar-arterial O_2 differences with special references to the distribution effect. J Appl Physiol 7:699-710, 1955

12. Sladen A: Discussion of "The effect of incremental PEEP on Pao_2 in patients with respiratory failure." Anesth Analg 52:214-215, 1973

13. Hedley-Whyte J, Pontoppidan H, Laver MB, et al: Arterial oxygenation during hypothermia. Anesthesiology 26:595-602, 1965

14. Singer MM, Wright F, Stanley LK, et al: Oxygen toxicity in man. A prospective study in patients after open-heart surgery. N Engl J Med 283:1473-1478, 1970

15. Dery R, Pelletier J, Jacques A, et al: Alveolar collapse induced by denitrogenation. Can Anaesth Soc J 12:531-557, 1965

16. Briscoe WA, Cree EM, Filler J, et al: Lung volume, alveolar ventilation and perfusion interrelationship in chronic pulmonary emphysema. J Appl Physiol 15:785-795, 1960

17. Downs JB, Mitchell LA, Dannemiller FJ, et al: Modification of airway closure and pulmonary gas exchange following open heart surgery. Crit Care Med 3:41, 1975

18. Ramachandran PR, Fairley HB: Changes in functional residual capacity during respiratory failure. Can Anaesth Soc J 17:359-369, 1970

19. West JB: Blood flow to the lung and gas exchange. Anesthesiology 41:124-138, 1974

20. Hedley-Whyte J, Corning H, Laver MB, et al: Pulmonary ventilation-perfusion relations after heart valve replacement or repair in man. J Clin Invest 44:406-416, 1965

21. Lopez-Majano V, Wagner HN, Twining RH, et al: Effect of regional hypoxia on the distribution of pulmonary blood flow in man. Circ Res 18: 550-557, 1966

22. Wilson RF, Larned PA, Corr JJ, et al: Physiologic shunting in the lung in critically ill or injured patients. J Surg Res 10:571-578, 1970

23. Lucas CE, Ross M, Wilson RF: Physiologic shunting in the lungs in shock or trauma. Surg Forum 19:35-37, 1968

24. Powers SR Jr, Burdge R, Leather R, et al: Studies of pulmonary insufficiency in nonthoracic trauma. J Trauma 12:1-14, 1972

25. Monaco V, Burdge R, Newell J, et al: Pulmonary venous admixture in injured patients. J Trauma 12:15-23, 1972

26. Balchum OJ, Jung RC, Turner AF, et al: Pulmonary artery to vein shunts, Current Research in Chronic Airway Obstruction. Proceedings of Ninth Annual Aspen Emphysema Conference, 1968, pp 223-238

27. Nomoto S, Berk JL, Hagen JF, et al: Pulmonary anatomic arteriovenous shunting caused by epinephrine. Arch Surg 108:201-204, 1974

28. Rahn H, Stroud RC, Tobin CE: Visualization of arterio-venous shunts by cinefluorography in the lungs of normal dogs. Proc Soc Exp Biol Med 80: 239-241, 1952

29. Strauss HW, Hurley PJ, Rhodes BA, et al: Quantification of right-to-left transpulmonary shunts in man. J Lab Clin Med 74:597-607, 1969

30. Tobin CE: Arteriovenous shunts in the peripheral pulmonary circulation in the human lung. Thorax 21:197-204, 1966

DISCUSSION

E. SCOTT McCORD, M.D.
Department of Anesthesiology
University of Missouri Medical Center
Columbia, Missouri

Dr. Douglas and his group should be congratulated on this most interesting paper. It points out that we should never become too satisfied with what we think is the truth, for more than likely someone will eventually show us that it wasn't really a truth at all.

In order to evaluate the ability of the lungs to oxygenate the blood one of the first steps is to measure the arterial O_2 tension (Pa_{O_2}). However, for this to have any real significance, one also needs to know the alveolar O_2 tension (PA_{O_2}). From these two, one can calculate the alveolar-arterial O_2 tension difference $P(A\text{-}a)O_2$. Even this, however, is not enough for thorough understanding of the situation because it tells us only a problem with oxygenation exists but nothing of what the problem may be. Intrapulmonary causes for an increase in $P(A\text{-}a)O_2$ may stem from an intrapulmonary right-to-left shunt ($\dot{Q}sp/\dot{Q}t$), ventilation/perfusion maldistribution ($\dot{V}_A/\dot{Q}$) and/or diffusion abnormalities.

The authors undertook this study in an effort to either confirm or deny reports in the recent literature that suggest a high concentration of inspired O_2 (FIO_2) may in itself increase the intrapulmonary shunt. Their goal was to define in a stepwise manner the actual change in $\dot{Q}sp/\dot{Q}t$, if any, that takes place with a changing FIO_2.

I would like to commend Dr. Douglas for the basic simplicity of the study. Small but often compounding errors are easily introduced into such studies and simplicity becomes very desirable. Many of these potential problems and sources for error have either been explained or otherwise accounted for by the authors and need no further mention. A couple of points, however, may be made here for emphasis.

It was stated that standard electrode technics were used, yet one of the problems in comparing various investigations is the definition of standard technic. Calibration of O_2 electrodes, handling of blood samples, and corrections for temperature variations in blood-gas and pH measurements, among others, seem to vary from study to study. Methods used to determine O_2 saturation also are of importance because of possible pH-independent changes in the O_2 dissociation curves.[1] This might alter mixed venous O_2 saturations if calculated from pH and $P\bar{v}O_2$ determinations alone.

Several questions are raised by this study. One has to wonder what effect longer exposure to O_2 would have on pulmonary shunting. Wolff and associates[2] reported a greater increase in $\dot{Q}sp/\dot{Q}t$ in trauma patients exposed to an FIO_2 of 0.83 than in those exposed to only 0.4 at the end of 48-72 hours. There were, however, no data to show whether the shunt varied with time. Another study[3] revealed no change in the shunt after 6-12 hours on 100% O_2, but direct comparisons here are not possible because it dealt with spontaneously breathing normal volunteers.

Two additional questions to be answered include: (1) what effect the presence or absence of preexisting chronic pulmonary disease might have on FIO_2 and measured shunting, and (2) how spontaneous versus mechanical ventilation might affect the relationship. McAslan's group[4] reported results very similar to those in the present study for patients without preexisting disease but a decreased shunt for patients who had preexisting chronic lung disease. This present study was rather remarkable in revealing no significant differences between either age groups or the various acute disease processes. While studying the effect of increasing FIO_2 on $P(A\text{-}a)O_2$, Cole and Bishop[5] along with others, reported an increased $P(A\text{-}a)O_2$ with an FIO_2 up to about 0.4. This remained fairly constant until the FIO_2 was 0.8, at which point the $P(A\text{-}a)O_2$ decreased with further increases in FIO_2.

On the surface, these data would appear to conflict with those in the present study. It must be remembered, however, that $P(A\text{-}a)O_2$ and $\dot{Q}sp/\dot{Q}t$, while often taken to represent the same thing, particularly with the FIO_2 is 1, are in reality not the same at all. At any rate, these 2 studies should not be compared directly because Cole and Bishop used spontaneously breathing normal volunteers. Nevertheless, it would be interesting to know the $P(A\text{-}a)O_2$ for Dr. Douglas' 30 patients at each FIO_2.

Whether this present paper becomes a definitive study, accurately describing the relationship between various levels of FIO_2 and pulmonary shunting, or whether it only defines a relationship existing between the patients studied under the conditions available and the technics used, can only be answered when others attempt to duplicate the results and when additional populations are studied. The ideal will be to define that FIO_2 (or range of FIO_2) that will create the smallest shunt while at the same time eliminate as much as possible any $\dot{V}_A/\dot{Q}$ disturbances.

It would appear that Dr. Douglas has added significantly to our knowledge of this area and has pointed out quite correctly what probably is a multifaceted etiology of

the changes observed. Several unanswered questions remain, however, which must be answered before the full relationship between F_{IO_2}, pulmonary shunting, $\dot{V}_A/\dot{Q}$ and $P_{(A\text{-}a)O_2}$ are fully defined.

REFERENCES

1. Shappell SD, Lenfant JM: Adaptive, genetic, and iatrogenic alterations of the oxyhemoglobin-dissociation curve. Anesthesiology 37:127-139, 1972

2. Wolff G, Gradel E, Rist M, et al: The effect of inspired oxygen concentration on intrapulmonary right to left shunt during postoperative mechanical ventilation. Br J Anaesth 44:350-353, 1972

3. Vandewater JM, Kagey KS, Miller JT, et al: Response of the lung to 6 to 12 hours of 100 percent oxygen inhalation in normal man. N Engl J Med 283:621-626, 1970

4. McAslan TC, Matjasko-Chiu J, Turney SZ, et al: Influence of inhalation of 100 percent oxygen on intrapulmonary shunt in severely traumatized patients. J Trauma 13:811-821, 1973

5. Cole RB, Bishop JM: Variations in alveolar-arterial O_2 tension difference at high levels of alveolar O_2 tension. J Appl Physiol 22:685-693, 1967

INTERNATIONAL CALENDAR

1976

October 18-20	Ljublajana, Yugoslavia: The Yugoslav Society of Anesthesiologists Meeting. For information: Dr. Stojan Jeretin, President, Ljublajana Clinical Center, Cae, Zaloska 7, Yugoslavia.
October 22-23	Copenhagen, Denmark: Dansk Anaesthesiologisk Selskab Meeting. For information: Dr. Erik Jacobsen, Righospitalet 9, Blegdamnsvej, DK-2100, Copenhagen, Denmark.
October 27-28	Antalya, Turkey: Turkish Society of Anesthesiology and Reanimation Meeting. For information: Prof. Sadi Sun, President, Cerrahpasa Hast, Istanbul, Turkey.
*October	Salisbury, Rhodesia: Society of Anaesthetists of Rhodesia Annual General Meeting, Gelfand Ritchken House. For information: Dr. N. Kaplan, President, c/o Dr. Daniel E. Borg, Harari Central Hospital, P.O. Box St. 14, Southerton, Salisbury, Rhodesia.
*October	Seoul, Korea: The Korean Society of Anesthesiologists Annual Meeting. For information: Dr. San Ho Jin, President, c/o Dr. Se Ung Chon, St. Mary's Hospital, Catholic Medical College, #1, 2Ka, Myong-Dong, Chung-ku, Seoul, Korea.
November 6	Taiwan, Republic of China: The Society of Anesthesiologists of the Republic of China Annual Meeting, Surgical Lecture Room. For information: Dr. Chi-Ching Chao, President, 1 Chang-Te St., 3 Taipei, Taiwan, Republic of China.
November 18-20	London, England: Assoc. of Anaesthetists of Great Britain and Ireland Meeting. For information: Dr. M. D. Vickers, Secretary, Room 475, Tavistock House, South, Tavistock Square, London WC1H 9JP, England.
December 8-10	Buenos Aires, Argentina, South America: Federacion Argentina de Association de Anestesiologists Meeting. For information: Dr. Hector Sanguinetti, President, Terrero 411, Buenos Aires, Argentina, South America.
December 26-30	Maharashtra State, India: Indian Society of Anaesthesiologists 26th Annual Conference. For information: Dr. A. I. Chruva, President, c/o Dr. N. K. Misra, I.M.A. Building, Medical Association Road, Patna-80004, India.
December 5-11	Belem, Para, Brazil: Society Brasileira de Anestesiologia 23rd Brazilian Congress of Anaesthesiology. For information: Dr. Joao Brenha Ribeiro, Rio de Janeiro, ZC-02, Guanabara, Brazil, South America.

Absence of Recall After General Anesthesia: Implications for Theory and Practice

STEVEN L. DUBOVSKY, MD*
ROBERT TRUSTMAN, PhD†
Denver, Colorado‡

To investigate the possibility that recall of auditory information occurs following general anesthesia, letter-word pairs were presented to 36 patients receiving light planes of general anesthesia for short operations. Postoperative testing which tapped auditory and visual memory demonstrated no evidence of recall. In a subsequent study, a single word was repeated during brief obstetric procedures in 12 patients. Postoperative testing was designed to maximize apparent recall. The only patient able to remember the experimental word had awakened during anesthesia. Even without the use of more sophisticated physiologic and psychologic measures of recall, the data presented indicate that, for all practical purposes, an adequately anesthetized patient does not remember information presented during surgery. Apparent recall probably indicates inadequate or uneven anesthesia. Anesthetic agents may interfere with memory formation by altering brain RNA or protein synthesis or electrochemical activity, or they may produce retrograde amnesia.

EVER since Crile[1] reported a patient who could repeat a discussion that occurred while she was anesthetized, there has been considerable controversy regarding whether or not the anesthetized patient can be aware of events occurring during surgery. It has recently been suggested that the advent of newer muscle relaxants and lighter planes of anesthesia have increased the likelihood of awareness during anesthetic procedures.[2-4] Many physicians have both hoped that optimistic remarks made during operations might have beneficial effects and been concerned that pessimistic remarks might have adverse effects on the patient's postoperative course. Case reports of physical[4] and psychologic[5] distress experienced by patients who have apparently overheard discouraging remarks made during surgery have increased this concern.

Since the use of interview data alone in uncontrolled studies has failed to provide good evidence of recall of information presented during anesthesia,[6-9] attempts have been made to use hypnosis[4,10] and physiologic measures of recognition of familiar material[10,11] to provide evidence that memory following general anesthesia does occur, even though the patient is not consciously aware of it.

Wolfe and Millett[12] and Hutchings[13] suggested postoperative comfort to unselected surgical patients at the completion of their operation, but before they were "awake." They reported that many patients responded to these suggestions by demonstrating less postoperative pain, nausea, and vomiting. It is unlikely, however, that the patients were truly anesthetized when they received the suggestions. It is also not known if the patients actually experienced less postoperative discomfort or, if knowing that they were experimental subjects, they simply complained less. Nursing staff may also have been more solicitous of patients whom they knew to be experimental subjects.

*Assistant Professor, Department of Psychiatry.
†Division of Psychology.
‡University of Colorado Medical Center, Denver, Colorado 80220.

Paper received: 12/1/75
Accepted for publication: 1/6/76

Pearson[14] attempted to deal with these questions with a double-blind placebo control design. Patients receiving, during surgical anesthesia, taped suggestions that they would be able to recover faster, were discharged 2.42 days sooner than placebo groups hearing music or nothing intraoperatively. A subsequent study of similar design, with the addition of electroencephalographic measurements to document depth of anesthesia while tapes were played, failed to confirm Pearson's findings.[15]

The present study applies a double-blind placebo-control design to the question of whether material presented during general anesthesia can be retrieved postoperatively. Simple, easy-to-learn experimental material is presented during light anesthesia, with tests of recall measuring subtle evidence of memory.

METHODS

After giving informed consent, patients aged 18 to 55, about to undergo elective surgery under general anesthesia, were told that the experimenters believed that auditory information could be learned during anesthesia, even though the patient remains asleep. It was suggested that the patients would be able to learn letter-word pairs presented during anesthesia, and recognize them on a postoperative test.

Eight letters chosen least frequently in a pilot study of letter guessing were selected as experimental letters. Two additional letters were arbitrarily chosen as "bogus" stimuli to be presented on a postoperative recognition test, but not presented experimentally. Nouns beginning with the letters chosen as stimulus letters were next paired with these letters. Subjects in a preliminary study were then asked to check from four choices the word that seemed to go best with each letter, e.g.,

"F" is for { Fire / Friend / Family / Food }

The 2 *least*-frequently checked words for each of the 8 stimulus letters (in this case, "Fire" and "Food") were paired with the letters in 2 experimental lists of alliterative letter-word pairs using Evans' method[16] of studying sleep learning. A placebo list of number-word pairs was prepared for the control group (table 1).

Cassette tapes of each list, lasting 15 minutes each, began with suggestions that although the patient was asleep, he would hear and remember the letter-word pairs on the tape. Repetitions of the stimuli followed, and the tape ended with repeated suggestions that the patient would remember the material presented. The tape for each subject was randomly selected and given to the anesthesiologist, who was unaware of its contents. The patient was anesthetized with a ± 1.3 MAC concentration of anesthetic. When the patient was judged clinically to be in a light plane of surgical anesthesia, the anesthesiologist began the tape, which was played in its entirety through earphones.

As soon after surgery as possible, recognition memory was tested by the experimenters, who were unaware of the contents of the tape to which the patient had been exposed. First, the patient was reminded that he had been exposed during anesthesia to letter-word combinations which he should be able to remember. Next, he was asked to look at a randomized alphabet and check any letters he thought he heard while anesthetized. At the same time, a tape recording of the same voice as that used during anesthesia read each letter in the sequence viewed by the patient, to aid auditory recognition.

Finally, the patient was presented with 10 separate pages, each containing a letter

TABLE 1

Paired Associates Presented During Anesthesia

List 1	List 2	List 3
G is for Game	G is for Glass	1 is for Joy
S is for Street	S is for Sugar	2 is for Room
H is for Health	H is for Hat	3 is for Book
F is for Food	F is for Fire	4 is for Water
M is for Market	M is for Measure	5 is for Table
E is for Effort	E is for Ear	6 is for Car
L is for Line	L is for Letter	7 is for Idea
N is for North	N is for Nest	8 is for Uncle

Lists 1 and 2 were presented to Experimental Groups I and II.

List 3 was presented to Placebo Group III.

and 4 words, and was asked to check the word he thought was paired with the letter presented during anesthesia. Again, a recording of the same voice played each choice aloud as the subject viewed it on the checklist. After each response, the subject stated his degree of certainty regarding his response using a 1-to-4 scale.[16] Two letter-word combinations not presented during anesthesia ("bogus" letters and words) were included to correct for guessing.

If retention and recognition of these stimuli had occurred, patients in experimental groups I and II would check more of the 8 experimental letters than did subjects in group III (placebo-control group). Subjects in group I would select more words from list 1 than subjects in group II or III. Subjects in group II would select more words from list 2 than subjects in group I or III. And subjects in groups I and II would express less certainty in choosing "bogus" words than words from their respective lists.

RESULTS

Most of the 36 patients underwent brief obstetric procedures, carried out under light anesthesia (table 2). Preoperative medication was atropine with or without diazepam in all patients.

Mann-Whiteney U tests[17] were calculated to compare recognition of letters and words presented during anesthesia vis-a-vis type of anesthetic received. These yielded U values of 36 for letter recognition and 33 for word recognition (not statistically significant by 2-tailed test). Therefore, the type of anesthetic received did not significantly influence apparent postoperative recognition of material presented during anesthesia. There was also no relationship between time-until-testing and apparent postoperative recognition of letters ($r_s = +0.31$; p=ns) and words ($r_s = +0.42$ and 0.12 for groups I and II; p=ns) presented during anesthesia.

On postoperative testing of letter recognition, the experimental groups failed to surpass the control group in number of experimental letters checked ($H = 3.72$; p=ns) suggesting that they did not recognize letters presented during anesthesia. In the selection of words from lists 1 and 2 by each group, group I did not recognize words from list 1 more frequently than group II or III, and group II did not recognize words from list 2 more frequently than group I or III (table 3). This is confirmed by simple analysis of variance of these scores (table 4). Subjects in groups I and II were therefore unable to recognize words presented to them during anesthesia more frequently than subjects who did not hear these words.

Subjects in the experimental groups were then compared for the average certainty they expressed in choosing relevant experimental words (list 1 for group I; list 2 for group II) versus bogus words on the post-operative recognition test. They expressed significantly higher average certainty on bogus items, and were not more certain in

TABLE 3

Number of Words from Lists 1 and 2 Chosen by Experimental and Control Subjects

Words	Total possible for each group	Number chosen by group I	Number chosen by group II	Number chosen by group III (control)
List 1 words	96	20	21	24
List 2 words	96	21	17	21

TABLE 2

Procedures and Anesthetic Agents

Group	Total number	Procedure			Anesthetic agents		
		Brief OB-Gyn*	Abdominal procedures†	Orthopedic procedures‡	Halothane and N_2O	Thiopental and N_2O	Enflurane and N_2O
Experimental group (I)	12	8	3	1	7	4	1
Experimental group (II)	12	10	1	1	6	5	1
Control group (III)	12	8	4	–	7	3	2
Total	36	26	8	2	20	12	4

*Dilatation and curettage, tubal ligation, cesarean section, therapeutic abortion, hysterectomy.

†Splenectomy, nephrectomy, cholecystectomy, herniorrhaphy.

‡Insertion of Zickel nail, removal of Küntscher rod.

TABLE 4

Simple Analysis of Variance Comparing Groups on Number of Words from List 1 and List 2 Chosen Postoperatively

List	Source	*SS*	*df*	*ms*	*F*	*p*
List 1	Total	45.64	35			
	Between groups	0.72	2	0.36	0.26	ns
	Within groups	44.92	33	1.36		
List 2	Total	40.31	35			
	Between groups	0.89	2	0.45	0.38	ns
	Within groups	39.42	33	1.19		

their choice of relevant experimental items (sign test [2-tailed] = 0.96 [negative comparisons] and 0.008 [positive comparisons]; $p = <.05$ for choice of bogus items). Groups I and II did not surpass controls in high-certainty selection (table 5).

Additional Study. — To investigate the possibility that too many stimuli were presented for anesthetized subjects to process, an additional study was devised presenting only 1 stimulus word. A tape beginning with the suggestion that the patient would remember the word that followed was presented to 12 patients undergoing D & C or tubal ligation. Next, the word "salami" was repeated every 5 seconds for 5 minutes, every 30 seconds for another 5 minutes, then again every 5 seconds for the remainder of the tape (total = 12 minutes). Postoperative recall was tested within 24 hours. Subjects were asked to choose the word they had heard during anesthesia as they looked at a list of 10 possible choices designed to maximize recognition of the experimental word and heard each word repeated on a tape recorder by the experimental voice.

Eleven subjects did not recognize the experimental word. The 12th subject said, "Don't even show me the choices: the word was *'salami.'* " She remembered awakening during anesthesia, and her anesthesiologist reported that in the middle of the procedure, she had opened her eys and winked at him. Our only evidence for postoperative recall occurred in a patient who was not fully anesthetized!

TABLE 5

Comparison of Words Chosen with High Certainty by Experimental and Control Groups

List	Group I	Group II	Group III	*H**	*p*
List 1 words	1	9	7	5.45	ns
List 2 words	2	7	7	2.40	ns

*Kruskal-Wallis analysis of variance by ranks.

DISCUSSION

Although the patients were presented with simple stimuli, and strong suggestions were given that they would be able to remember the stimuli, they were not strongly motivated to do so. Learning under any circumstance is known to be facilitated by motivational factors[18] such as hunger.[19] It is also well known that information which is meaningful[2,9] and is associated with strong emotion[18,19] is easier to remember. Meaningful, emotionally laden words occurring in the context of a motivational state (the wish to get well) might well be more likely to be remembered. While the creation of bogus "crises" during operation in one study[20] satisfied these conditions, good controls are impossible to devise, and serious ethical difficulties are created.[2] Apparent recall of emotionally laden words or words of particular significance to the patient, such as names of family members, would be complicated by the probability that patients would be exposed to them perioperatively.

Our method of testing memory needs also to be carefully considered. Although recognition memory is a sensitive measure of recall,[10,16] auditory stimuli may influence a patient even though he does not remember them consciously.[3,4,9] It is possible that hypnosis, which is said to be a tool for recovering such unconscious memories[3,4,9,11,21] and has been used in studies of apparent recall following anesthesia,[2] would have provided evidence of recall. The use of hypnosis as an adjunctive investigative tool, however, raises the possibility that the hypnotist

is suggesting the correct answer to the subject subliminally, complicating interpretation of the data. Also, not all patients are equally hypnotizable and differences in apparent recall may reflect differences in depth of hypnosis during testing.

An even more elegant method of testing unconscious recognition of significant information employs the observation that heart rate decreases when attention is directed to a familiar or important stimulus, even when there is no verbal report of recognition of the stimulus.[10] Measuring heart rate or some other physiologic measure of attention[9] might have provided some evidence of postoperative recall. However, the interpretation of such measures would be complicated by the physiologic effects of the anxiety of hospitalization and surgery and of various medications.

A final possibility is that the anesthetized state has cueing properties which need to be reintroduced to truly test recall.[22] If such state-dependent learning[23] did occur, the patient would only recall stimuli presented during anesthesia while under repeated anesthesia. Even if this were possible, it would be difficult to demonstrate and would not be of clinical importance.

We used methods which maximize learning and recognition. The one patient who was not fully anesthetized showed obvious learning and instantaneous recall of the test word, in spite of the distractions of the operating room. Despite the objections discussed above, our measures are probably the best available for clinically practical purposes.

The Psychobiology of Postanesthetic Amnesia.—The 2-stage theory of memory, first proposed by Hebb,[22] holds that memory traces are laid down in the form of short-term reverberatory electric circuits which may, during the process of consolidation, be fixed to produce long-term memory. The process by which permanent memory traces ("engrams") are formed has been said to involve DNA-dependent RNA or protein synthesis[19,24] changes in brain biogenic amines,[19] synaptic changes in memory circuits,[19] the formation of permanent reverberating electric circuits,[19,23] and structural or functional growth of neuronal and glial elements throughout the brain.[19] Anesthesia may act at one or many of these loci.

Anesthetic agents might interfere with the formation of the engram by blocking RNA synthesis. This has been shown in the rat to interfere with ongoing learning without disrupting previously learned behavior.[24] Ether has been shown to produce "localized seizures" which may interfere with short-term memory consolidation in animals.[18,25] A similar mechanism in man may interfere with the storage of information as cerebral electrical activity,[18,19] and many anesthetics have in fact been shown to depress EEG activity.[26] Anesthesia may also interfere with reverberating circuits by blocking polysynaptic transmission,[19] or it may disconnect the limbic-system and RAS input which add significance to information to be stored.[19] Indeed, "some of the experiments using anesthetics . . . confirm that interruption of brain activity (electrical or chemical) shortly after a learning experience impairs the memory of that experience."[23a] Atropine[18] and other anticholinergics,[19] and other premedicants, especially diazepam,[10] may further disrupt memory consolidation by altering electrocortical activity in as-yet-unknown ways.

Most studies of the effects of drugs on memory have been carried out in animals,[18] and the possibility that anesthetics interfere with retrieval of complex information in man is difficult to assess. It has been shown, however, that a variety of agents, including barbiturates, ether, transcortical electric shock, and flurothyl produce retrograde amnesia for conditioned responses in animals.[18] It is possible that learning in man may occur during anesthesia, but that the information learned is then unavailable or forgotten.

CONCLUSIONS

Whatever the possible mechanism of action, our findings suggest that recall following anesthesia does not occur. Many of our patients received light anesthesia of brief duration without evidence of recall. The fact that only a patient who was not fully anesthetized demonstrated unequivocal recall leads us to suspect that in previous studies which have demonstrated apparent recall following anesthesia, experimental material was presented when the patients were not truly anesthetized. It would be wise to bear in mind that many drugs used as adjuncts to general anesthesia, such as droperidol,[27] may disrupt the patient's initiative to complain, making him appear to be anesthetized even though he is awake. Patients experiencing such "cerebral curarization"[27] would of course remember and react to information presented during surgery.

The clinical implications of our findings are apparent. If care is taken that patients are fully anesthetized, discussion of clinical aspects of the patient's case in the operating room need not be curtailed, and attempts at promoting healing through verbal suggestion during surgery will probably not be successful. Evidence of apparent recall following anesthesia should alert the physician to the possibility that his patient has not been truly anesthetized, that a fluctuating depth of anesthesia is resulting in intermittent alertness, or that he is making remarks either before the patient is anesthetized or after he is awake.

ACKNOWLEDGMENT

The authors would like to thank Dr. Henry Casson for his help with the project and the preparation of the manuscript, and Dr. William Droegemueller for his very kind assistance with patient material.

REFERENCES

1. Crile G: George Crile: An Autobiography. Philadelphia, JB Lippincott Company, 1947

2. Scott DL: Awareness during general anaesthesia. Can Anaesth Soc J 19:173-183, 1972

3. Ayre P: Awareness during anaesthesia. Br Med J 2:117, 1969 (ltr to ed)

4. Cheek D, Le Cron L: Clinical Hypnotherapy. New York, Grune & Stratton, Inc, 1968

5. Hewer C: Thoughts on Modern Anaesthesia; A Critical Appraisal of Some Aspects of Present-day Practice. London, Churchill, Ltd, 1970

6. Wilson J, Turner D: Awareness during cesarean section under general anaesthesia. Br Med J 1:280-283, 1969

7. Faithfull N: Awareness during anaesthesia. Br Med J 2:117, 1969 (ltr to ed)

8. Taub HA, Eisenberg L: A comparison of memory under three methods of anaesthesia. Can Anaesth Soc J 22:298-306, 1975

9. Lewis S, Jenkinson J, Wilson J: An EEG investigation of awareness during anaesthesia. Br J Psychol 64:413-415, 1973

10. Cheek D: Unconscious perception of meaningful sounds during surgical anesthesia as revealed under hypnosis. Am J Clin Hypn 1:101-113, 1959

11. Spence DP, Lugo M, Youdin R: Cardiac correlates of cognitive processing. Psychosom Med 36:420-437, 1974

12. Wolfe L, Millett J: Control of post-operative pain by suggestion under general anesthesia. Am J Clin Hypn 3:109-112, 1960

13. Hutchings D: The value of suggestion given under anesthesia: a report and evaluation of 200 consecutive cases. Am J Clin Hypn 4:26-29, 1961

14. Pearson R: Response to suggestions given under general anesthesia. Am J Clin Hypn 4:106-114, 1961

15. Abramson M, Greenfield I, Heron W: Response to or perception of auditory stimuli under deep surgical anesthesia. Am J Obstet Gynecol 96:584-585, 1966

16. Evans F: Hypnosis and sleep: techniques of exploring cognitive activity during sleep, Hypnosis: Research Developments and Perspectives. Edited by E Fromm, R. Shor. Chicago, Aldine-Atherton, 1972

17. Siegel S: Non parametric Statistics for the Behavioral Sciences. New York, McGraw-Hill Book Company, Inc, 1956

18. Michel'Son MY, Longo VG: Pharmacology of Conditioning, Learning and Retention. New York, The Macmillan Company, 1965

19. Pribram KH, Broadbent DE: Biology of Memory. New York, Academic Press, 1970

20. Levinson B: States of awareness under general anaesthesia: primary communication. Br J Anaesth 137:544-546, 1965

21. Cooper L, Hoskovec J: Hypnotic suggestions for learning during stage I REM sleep. Am J Clin Hypn 15:102-111, 1972

22. Hebb DO: The Organization of Behavior; a neuro-psychological theory. New York, Wiley, Inc, 1949

23. Gibbs ME, Mark RF: Inhibition of Memory Formation. New York, Plenum Press, 1973

23a. Ibid, p 45

24. Brill H, Cole J, Demker P, et al: Neuropsycho-Pharmacology. Amsterdam, Excerpta Medical Foundation, 1967

25. Alporn HP, Kimble DP: Retrograde amnesic effects of diethyl ether and bis (trifluoroethyl) ether. J Comp Physiol Psychol 63:168-171, 1967

26. Faulconer A Jr, Bickford RG: Electroencephalography in Anesthesiology, Springfield, Illinois, Charles C Thomas, Publisher, 1960

27. Boulanger M: A propos d'un case de "curarization cérébrale." Can Anaesth Soc J 19:198-199, 1972

Effect of Morphine-Diazepam on Signs of Anesthesia, Awareness, and Dreams of Patients Under N_2O for Cesarean Section

EZZAT ABOULEISH, MB, BCh, MD*
FLOYD H. TAYLOR, ScD†
Pittsburgh, Pennsylvania

Morphine (0.2 mg/kg) and diazepam (0.1 mg/kg) were injected IV after delivery of the fetus in 68 parturients undergoing cesarean section (CS). General anesthesia was with thiamylal-N_2O-O_2 (4:2) and muscle relaxant. Twenty-four to 36 hours postoperatively, 1 patient had recall, 1 had unpleasant dreams, and 2 had pleasant dreams. The incidence of recall and unpleasant dreams was 3.8 percent in elective CS and 0 percent in emergency cesareans. Morphine-diazepam combination caused anterograde and retrograde amnesia. During the cesarean, movement of patient, size of pupils, or changes in blood pressure were not indicative of awareness or dreams. During anesthesia, 33 percent O_2 produced adequate oxygenation of mother and fetus.

AWARENESS, pain, and/or unpleasant dreams constitute *undesirable side effects of light anesthesia* (USELA). The incidence of USELA during N_2O-O_2-muscle relaxant anesthesia for cesarean section (CS) is 36.1 percent in elective and 17.3 percent in emergency CS.[1] To reduce USELA, various measures have been attempted: injection of 0.6 mg of IV hyoscine before induction,[2] or adding halothane,[3] methoxyflurane,[4] or trichloroethylene[5] to N_2O-O_2. The combination of morphine and diazepam to supplement N_2O was also found to have amnesic effects in male surgical patients.[6,7] The purpose of our study was to evaluate such a combination in cesarean section.

METHODS

Since the incidence of USELA using N_2O alone is high and well documented, it was considered unfair to subject more patients to such a technic. Therefore, in this study, Wilson's series[1] was used as the control. This study group consisted of 68 patients undergoing cesarean deliveries, 53 of which were elective, under general anesthesia. Patients having had a narcotic within 6 hours, with respiratory or valvular cardiac disease, or a history of alcohol or drug addiction were excluded from the study. The possibility of awareness or dreams during the procedure was not discussed preoperatively with the patient, to eliminate suggestion and expectation, and no premedication was administered.

On arrival in the operating room (OR), an IV cannula was inserted in the patient's hand or forearm and an infusion was started. Blood pressure (BP) and pulse rate were measured, left uterine displacement device was placed, an ECG monitor was applied, and O_2 by facemask was administered. Two minutes before induction, 0.4 mg of atropine and 3 mg of curare were injected. Just before abdominal incision, anesthesia was induced by 4 mg/kg of thiamylal, cricoid pressure was applied, and 1.5 mg/kg of succinylcholine chloride (SCC) was injected,

*Associate Professor of Clinical Anesthesiology, University of Pittsburgh School of Medicine; Director, Obstetric Anesthesia, Magee-Womens Hospital, Pittsburgh, Pennsylvania 15213.

†Associate Research Professor of Community Medicine, University of Pittsburgh School of Medicine.

Paper received: 11/13/75
Accepted for publication: 2/5/76

followed by endotracheal intubation with a cuffed tube. Anesthesia was maintained until the end of operation with N_2O-O_2 (67:33) plus muscle relaxant. F_{IO_2} was continuously monitored using an IL 404 Oxygen Alarm System,* and ventilation was manually controlled. The muscle relaxants used were SCC in 43, curare in 22, and pancuronium in 3 cases.

Immediately after delivery, 0.2 mg/kg of morphine and 0.1 mg/kg of diazepam were separately administered to a maximum of 15 and 7.5 mg respectively by injection into the tubing of rapidly administered 5 percent dextrose solution containing 10 units of oxytocin per liter.

At the time of delivery, maternal arterial and fetal umbilical-vein blood gases were determined in 25 cases. Unless the BP and/or pulse changes required minute-to-minute surveillance, they were checked and recorded every 5 minutes. BP was measured by indirect auscultation and pulse rate was counted at the brachial artery. Any movement of the patient, the surgical step at which movement occurred and the part of the body moved, and the size and reaction of the pupils before and after administration of morphine-diazepam, were recorded.

At 24 to 36 hours postoperatively, patients were asked: (1) What was the last thing you remember before going to sleep? (2) What was the first thing you remembered on waking? (3) Do you remember anything between going to sleep and waking? (4) While you were sleeping, during the operation, did you dream? If yes, was the dream pleasant, unpleasant, or indifferent? (5) Do you usually remember your dreams vividly? (6) Have you ever had experience with alcohol? If yes, was the experience pleasant, unpleasant, or indifferent? (7) Have you ever had experience with drugs, such as LSD, "speed," Marijuana, etc? Was the experience pleasant, unpleasant, or indifferent? (8) If you must have another operation, would you like the same anesthetic or not, and why?

*Sensorlabs, Division of Instrumentation Laboratories, Inc, Lexington, Massachusetts.

RESULTS

None of the 15 emergency patients had any recall or dreams during CS. In the 53 elective cases, 1 patient reported painless awareness of the abdominal incision, 1 had unpleasant, and 2 had pleasant dreams. Thus, the total number of patients having USELA was 2 (3.8%), a statistically significant ($p>0.01$) reduction over Wilson's series[1] (table 1).

Owing to difficulty in intubation, the induction-incision and induction-delivery times were much prolonged in patients with USELA compared with those who had no recall (table 2). However, the duration of operation in both groups was not markedly different.

During operation, 45 patients moved, of whom 42 had no recall, 2 had USELA, and 1 reported pleasant dreams. There was no correlation between the incidence of movement and the type of muscle relaxant. Under SCC drip, there was no specific surgical step at which patients moved. When a nondepolarizing muscle relaxant was used instead, 75 percent of the patients moved during closure of the subcutaneous tissue or skin.

During CS, there was no change in BP equal to or more than 50 percent of the original level. In 52 cases, BP changes were less than 25 percent. While 8 patients showed a 25 percent rise of BP, yet another 8 had more than 25 percent fall, mostly

TABLE 1

Awareness and Unpleasant Dreams in Cesarean Section with Morphine-Diazepam Supplementation of N_2O Anesthesia

	Elective CS		Emergency CS		Total CS	
	Wilson's series[1]	Study	Wilson's series[1]	Study	Wilson's series[1]	Study
Number of patients	61	53	75	15	136	68
Incidence of						
Awarness or pain (%)	16.4	1.9*	4.0	0*	9.6	1.47*
Unpleasant dreams (%)	19.7	1.9*	13.3	0*	16.2	1.47*
USELA (%)	36.1	3.8*	17.3	0*	25.8	2.9*

*Significantly different ($p<0.01$).

TABLE 2

Time Relationships of Awareness and Procedures
(± SEM)

	Induction-incision time* Mean	Induction-delivery time* Mean	Duration of Operation* Mean
No awareness, n = 64	2.6 (±0.2)	11.4 (±0.8)	71.5 (±5.1)
USELA			
Aware, n = 1	7.0	36.0	77.0
Unpleasant dream, n = 1	5.0	25.0	70.0
Pleasant dreams, n = 2	2.5 (±0.5)	13.0 (±2.0)	60.5 (±6.5)

*Minutes.
n = number of patients in each group.

after IV diazepam, morphine, and oxytocin drip.

During operation, the pupils of all patients were reactive to light: the more dilated the pupils, the more brisk the reaction. Before morphine-diazepam injection, 44 patients had dilated pupils. After morphine-diazepam administration, 9 patients, who had no recall or dreams, continued to have dilated pupils.

There was no apparent correlation between USELA and patient physical status, vivid remembrance of dreams, or experience with alcohol or drugs.

All patients recalled the events occurring in the OR before induction. Although 85 percent answered questions rationally before leaving the OR, only 9 percent remembered events before reaching the recovery room. The first event recalled by 65 percent of the mothers was related to their babies, e.g., sex and/or weight of the baby. Sixty-five patients considered recovery from anesthesia to be pleasant and smooth; 2 complained of abdominal pain and sore throat, and 63 (93%) would like to have the same anesthetic procedure if another operation is needed. There were no signs of maternal hypoxia, and the condition of the baby was dependent on its preoperative state rather than on the anesthetic technic.

DISCUSSION

An early report[8] described the use of diazepam for CS as disappointing. Preoperative oral and IM diazepam administration increased the incidence of USELA. A later study[9] reported that the preoperative administration of diazepam, narcotic, and/or scopolamine produced adequate amnesia, but the combination of the 3 drugs produced marked respiratory and circulatory depression. However, in our study, using only 2 drugs, diazepam and morphine, in the recommended dosage, no patient required postoperative ventilatory assistance. In fact, most were able to move themselves from the operating table to the recovery room bed.

The absence of significant cardiovascular depression due to morphine-diazepam was evidenced by the limited number of cases that showed hypotension despite the inclusion of emergency cases, and the limited decrease in BP despite the use of oxytocin. The safety of the use of morphine-diazepam in poor-risk surgical patients has also been reported.[6] Diazepam has been shown to result in anterograde amnesia by accelerating decay of the memory trace, thus impairing its consolidation.[10,11] From our study, diazepam together with morphine give both anterograde and retrograde amnesia.

One of the reported disadvantages of diazepam is venous thrombosis at the site of injection.[12] The absence of such a complication in our series may be due to the injection of 2.5-mg increments of diazepam into a rapidly infused solution. The vasodilative action of oxytocin[13] may have been a contributing factor against venous thrombosis. At term, the minimal alveolar concentration (MAC) of inhalation anesthetics is reduced by 25 to 40 percent.[14] Since both diazepam and morphine reduce the MAC of general anesthetics,[15-17] the use of morphine-diazepam during CS could have decreased USELA by further reducing the MAC of N_2O.

With increasing concentration of N_2O, spontaneous movements began at a concentration of 60 percent and increased with higher concentrations.[18] In our study, there

was no apparent correlation of movement with awareness, pain, or dreams, but rather with the degree of paralysis. Neither changes in BP nor pupil size were indicative of awareness or dreams. Our conclusion is that these changes are autonomic in origin, determined by the tone of the autonomic nervous system, modified by drug administration, and should not be relied on for evaluating the depth of anesthesia during N_2O administration.

The level of thiamylal in maternal blood falls steeply during the first 4 minutes following an IV bolus of 4 mg/kg.[19] During that period, there must be a buildup of a sufficient concentration of inhalation agent to take over from the waning effect of the agent. If intubation is difficult and induction time is prolonged, as occurred in 2 of our patients, awareness may occur. Therefore, with such difficulties, a second 1.3-mg/kg dose of thiamylal is advisable, and N_2O-O_2 should be administered for about 2 minutes before incision. The combination of these 2 doses of thiamylal has no depressant effect on the fetus.[19]

As reported above, the first event recalled by most mothers during recovery from anesthesia concerned their babies. The auditory and visual information of high emotional content results in memory consolidation to permit recall.[20] The only patient who had complete amnesia of her stay in the recovery room had her baby placed for adoption.

ACKNOWLEDGMENT

We thank Miss Lois Sprague and Miss Kathy Kutzavitch for secretarial assistance.

REFERENCES

1. Wilson J, Turner DJ: Awareness during caesarean section under general anaesthesia. Br Med J 1:280-283, 1969

2. Crawford JS: Awareness during operative obstetrics under general anaesthesia. Br J Anaesth 43:179-182, 1971

3. Moir DD: Anaesthesia for caesarean section: an evaluation of a method using low concentrations of halothane and 50 percent of oxygen. Br J Anaesth 42:136-142, 1970

4. Crawford JS, Burton M, Davies P: Anaesthesia for section: further refinements of a technique. Br J Anaesth 45:726-732, 1973

5. Crawford JS, Davies P: A return to trichloroethylene for obstetric anaesthesia. Br J Anaesth 47:482-490, 1975

6. Eisenberg L, Kwan AM: Neuroleptanaesthesia with diazepam-morphine in poor-risk surgical patients. Can Anaesth Soc J 18:465-472, 1971

7. Eisenberg L, Taub HA, Burana A: Memory under diazepam-morphine neuroleptanesthesia in male surgical patients. Anesth Analg 53:488-495, 1974

8. Turner DJ, Wilson J: Effect of diazepam on awareness during caesarean section under general anaesthesia. Br Med J 2:736-737, 1969

9. Pandit SK, Dundee JW, Keilty SR: Amnesia studies with intravenous premedication. Anaesthesia 26:421-428, 1971

10. Clark PRF, Eccersley PS, Frisby FP, et al: The amnesic effect of diazepam (Valium). Br J Anaesth 42:690-697, 1970

11. Grove-White IG, Kelman GR: Effect of methohexitone, diazepam and sodium 4-hydroxybutyrate on short-term memory. Br J Anaesth 43: 113-116, 1971

12. Padfield A: Thrombosis following diazepam (correspondence). Br J Anaesth 46:413, 1974

13. Johnstone M: The cardiovascular effects of oxytocic drugs. Br J Anaesth 44:826-834, 1972

14. Palahniuk RJ, Shnider SM, Eger EI II: Pregnancy decreases the requirement for inhaled anesthetic agents. Anesthesiology 41:82-83, 1974

15. Perisho JA, Buechel DR, Miller RD: The effect of diazepam (Valium) on minimum alveolar anaesthetic requirement (MAC) in man. Can Anaesth Soc J 18:536-540, 1971

16. Tsunoda Y, Hattori Y, Takatsuka E, et al: Effects of hydroxyzine, diazepam, and pentazocine on halothane minimum alveolar anesthetic concentration. Anesth Analg 52:390-394, 1973

17. Fraioli RL, Sheffer LA, Steffenson JL: The MAC equivalent of morphine. American Society of Anesthesiologists, Abstracts of Scientific Papers, 1973, p 253

18. Parbrook GD: The levels of nitrous oxide analgesia. Br J Anaesth 39:974-982, 1967

19. Kosaka Y, Takahashi T, Mark LC: Intravenous thiobarbiturate anesthesia for cesarean section. Anesthesiology 31:489-506, 1969

20. Cherkin A, Harroun P: Anesthesia and memory processes. Anesthesiology 34:469-474, 1971

Relation of $Paco_2$ to Fresh Gas Flow in a Circle System

KANCHAN PATEL, MD*
EDWARD J. BENNETT, MD†
ERNEST M. GRUNDY, FFARCS‡
ARTEMIO IGNACIO, JR, MD§
Chicago, Illinois‖

Recent reports have described methods of controlling the level of CO_2 during anesthesia with a N_2O-relaxant sequence and controlled ventilation. This paper describes a method of predicting and controlling the $Paco_2$, using body weight for determination of the fresh gas flow from the anesthetic machine, removing the absorbent from the canister while leaving the canister in the circuit, and controlling ventilation at 12 ml/kg and at 12/min.

THERE is a tendency to use the terms hypocapnia and hyperventilation synonymously,[1] but the terms are not quite the same. It is possible to overventilate a person with a mixture containing CO_2, with resultant hypercapnia. Thus, hyperventilation can be defined more accurately as pulmonary ventilation in excess of that required to keep blood $Paco_2$ within desired limits.

The dangers of mechanical ventilation of the paralyzed patient are those of underventilation or overventilation and hypercapnia or hypocapnia. Because the problems of hypercapnia are well appreciated, there is a tendency to overventilate; the result usually is an undesirable and even detrimental degree of hypocapnia. The ideal appears to be to keep $Paco_2$ in the low normal range, 35 to 40 torr.

The purpose of this study was to determine whether $Paco_2$ could be controlled easily and simply by limiting the fresh gas flow (FGF) into a circle system without soda lime in the absorber, thus controlling $Paco_2$ independently of ventilation.

A recent report showed that $Paco_2$ could be accurately predicted and controlled by using the Nunn blood-gas predictor, setting the FGF at the same numerical value as the predicted alveolar ventilation ($\dot{V}_A$) to obtain the required $Paco_2$.[2] In the present study, FGF was related to body weight, with the amount of mechanical ventilation always kept in excess of FGF.[3] Under these circumstances, CO_2 elimination from the whole circuitry (patient + anesthetic system), was through the exhaust valve and at a rate proportional to the FGF from the machine.[2]

METHODS

Patients (table 1) were selected from the elective schedule for major abdominal operations. Most were in ASA categories I-III, and informed consent was obtained. Arterial cannulation was employed for monitoring during the study. Premedication consisted

*Assistant Professor.
†Professor.
‡Assistant Professor.
§Assistant Professor.
‖Department of Anesthesiology, University of Illinois Hospitals, Chicago, Illinois 60612.

Paper received: 12/1/75
Accepted for publication: 1/28/76

TABLE 1

Patient Data

Number of patients		28
Male	15	
Female	13	
Age		
Mean	54 yr	
Range	15-80 yr	
Weight		
Mean	70 kg	
Range	40-96 kg	

of atropine with morphine, diazepam, or hydroxyzine IM 45 minutes before induction. Anesthesia was induced with a hypnotic dose of sodium thiopental followed by 120 mcg/kg of pancuronium and controlled ventilation was with N_2O 60 to 70 percent in O_2. Following topical anesthesia of the larynx and trachea, patients were intubated endotracheally with a snug-fitting cuffed plastic disposable tube. Ventilation was then instituted with a bellows-type mechanical ventilator (Air Shields Ventimeter®). The tidal volume (V_T) was set at 12 ml/kg at a respiratory rate of 12/min. V_T and minute volume ($\dot{V}_E$) were checked frequently on the expiratory side with a Wright respirometer, which was not left in the circuit. Anesthesia was supplemented with droperidol and fentanyl as indicated by the patient's vital signs.

The circle system was used without soda lime in the cannister but with the cannister left in the circuit. The FGF into the circuit and the spill valve for excess gases were separated from the patient by the inspiratory and expiratory valves.[4]

After 30 minutes with any FGF, blood gases were checked on an Instrumentation Laboratories IL 313 Blood Gas Analyzer, calibrated before every reading, and analyzed by the same technician using the same collection technic for each analysis. F_{IO_2} was monitored with a Teledyne® O_2 analyzer and kept constant throughout the procedure at 0.3 or 0.4, whichever was more appropriate. Keeping the ventilation constant, FGF was progressively lowered from 120 to 100, to 80, 60, and then 40 ml/kg/min. At each setting, 30 minutes was allowed for establishing a steady state; then measurements were taken as before. At the end of this part of the investigation, $\dot{V}$ varied from half to double that used earlier but was always greater than FGF, and blood gases were determined as before.

For full utilization of FGF, $\dot{V}$ must exceed FGF, to prevent possible reduction of V_T to where dead-space gas ventilation would result. In this study, to determine the role of $\dot{V}$, the rate and volume of ventilation were altered between 50 and 200 percent of those used earlier, with V_T always >5 ml/kg.

RESULTS

At the range of gas flow tested (120 to 40 ml/kg/min), $Paco_2$ ranged from 29.1 ± 3.4 to 46.2 ± 4.6 (table 2 and figure) and Pao_2 from 125 to 135 torr. The amount of ventilation did not change the readings obtained for $Paco_2$. Several different ventilators were used; results were similar so long as the ventilator was of the type colloquially termed an "automatic bag squeezer."

DISCUSSION

It has been predicted[5] that $Paco_2$ would be determined by the FGF into the particular anesthetic circuitry rather than by $\dot{V}_A$,

TABLE 2

Fresh Gas Flow Related to Blood-Gas Tension

Fresh gas flow, ml/kg/min	$Paco_2$ mean ± 1 SD torr	Pao_2, torr
120	29.1 ± 3.4	125
100	31.3 ± 3.1	114
80	34.4 ± 3.1	133
60	38.4 ± 3.3	134
40	46.2 ± 4.6	135
10 L/min	26.3 ± 3.0	134

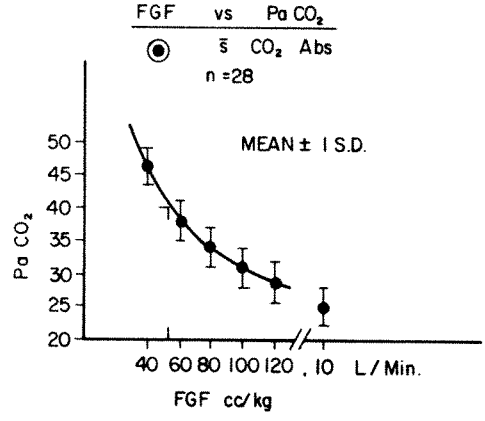


FIGURE. Relation of $Paco_2$ to fresh gas flow from machine.

even though the latter would be vital to proper ventilation. When closed-circle systems used cyclopropane or halothane, hyperventilation was avoided. But current technics employing N_2O supplemented by relaxants and narcotics require controlled ventilation.

In FGF into a semiopen system, using a Mapleson D modification, the flow needed for normocarbia was 100 ml/kg/min.[6] Using a Bain circuit, a flow of 70 ml/kg/min resulted in a $Paco_2$ of approximately 40 torr, provided the $\dot{V}_E$ was higher than the FGF.[7] At a V_T of 10 ml/kg, a slightly lower $Paco_2$ was achieved in another study with the Bain circuit (36.6 torr)[8] and the same flow rate. In yet another study,[2] using the Nunn blood-gas predictor, an instrument that provides data for CO_2 production and respiratory quotients under anesthesia,[3] FGF was set at the same numerical value as the predicted $\dot{V}_A$ to obtain normocarbia.

The concept that FGF from the machine determines $Paco_2$ has been developed further in that, under conditions of rebreathing, hyperventilation cannot alter the alveolar gas composition, which is determined by gas exchange, flow rate, and the composition of the fresh gas.[9]

Results from the present study will be valid if the FGF and the spill of excess gases are separated from the patient by the inspiratory and expiratory valves, and if V_T is not reduced below 5 ml/kg. The FGF shown does not appear to change with the respiratory status of the patient in the level of $Paco_2$ obtained, although O_2 will be affected. This type of control of $Paco_2$ will allow the Pao_2, $Paco_2$, and the pattern and type of ventilation to be varied independently of one another and tailored to suit the particular requirements of individual patients.

A problem of controlled ventilation during N_2O anesthesia has been that reducing the ventilation in order to lessen the degree of hypocapnia also tends to reduce Pao_2 levels. The other methods of increasing $Paco_2$ by adding dead space or by adding CO_2 to inspired gases do not appear to be widely used. Thus a method of predicting $Paco_2$ and then controlling it during anesthesia appears useful.

Removal of the CO_2 absorbent from the circuit (or elimination of the CO_2 absorber circuit in machines so equipped) will allow:

1. Better control of $Paco_2$ by varying FGF
2. No inhalation of dust (soda lime)[10]
3. No absorber exhaustion
4. No problem of soda lime/agent incompatibility
5. No bacterial colonization[11]
6. No added resistance in the cricuit

If, at any time, the limitation of gas flow is deemed unsuitable, the circle can be temporarily converted to a virtual nonrebreathing circuit by increasing the FGF.

REFERENCES

1. Utting JE: Hypocapnia, General Anesthesia. Third edition. Edited by TC Gray, JF Nunn. London, Butterworths, 1971, volume 1, chapter 12, pp 181-184

2. Scholfield EJ, Williams NE: Prediction of arterial carbon dioxide tension using a circle system without carbon dioxide absorption. Br J Anaesth 46:442-445, 1974

3. Suwa K, Yamamura H: The effect of gas inflow on the regulation of CO_2 levels with hyperventilation during anesthesia. Anesthesiology 33: 440-445, 1970

4. Eger EI II: Anesthetic systems: construction and function, Anesthetic Uptake and Action. Baltimore, Williams & Wilkins Company, 1974, chapter 13, pp 206-227

5. Mapleson WW: The elimination of rebreathing in various semiclosed anaesthetic systems. Br J Anaesth 26:323-332, 1954

6. Baraka A: Pco_2 control by fresh gas flow during controlled ventilation with a semi-open circuit. Br J Anaesth 41:527-530, 1969

7. Bain JA, Spoerel WE: Flow requirements for a modified Mapleson D system during controlled ventilation. Can Anaesth Soc J 20:629-636, 1973

8. Henville JD, Adams EF: Assessment of the Bain anaesthetic system during controlled ventilation. Br J Anaesth 47:1024, 1975

9. Nunn JF, Newman HC: Inspired gas, rebreathing apparatus dead space. Br J Anaesth 36:5-10, 1964

10. Debban DG, Bedford RF: Overdistention of the rebreathing bag, a hazardous test for circle-system integrity. Anesthesiology 42:365-366, 1975

11. Dryden GE: Uncleaned anesthetic equipment. JAMA 233:1297, 1975

A Comparative Interaction of Epinephrine with Enflurane, Isoflurane, and Halothane in Man

RICHARD R. JOHNSTON, MD*
EDMOND I. EGER, II, MD†
CHARLES WILSON, MD‡
San Francisco, California§

Forty-eight patients undergoing transphenoidal removal of pituitary tumors received submucosal injections of epinephrine in saline solution during halothane, enflurane, or isoflurane anesthesia. Twelve additional patients received epinephrine in 0.5 percent lidocaine while anesthetized with halothane. Positive evidence of ventricular irritability was given by the appearance of 3 or more premature ventricular contractions during or following injection. Positive or negative responses were plotted against the total dose of epinephrine in μg/kg body weight. From these data, the dose producing a positive response in 50 percent of patients (ED_{50}) was calculated. An ED_{50} of 2.1 μg/kg for halothane, 3.7 μg/kg for halothane-lidocaine, 10.9 μg/kg for enflurane, and 6.7 μg/kg for isoflurane indicates the relative safety of these agents when epinephrine is injected for hemostasis. The data also suggest that lidocaine given with the epinephrine protects against ventricular arrhythmias.

PREVIOUS studies in dogs suggested that isoflurane is compatible with epinephrine, while conflicting data suggest that enflurane, an isomer of isoflurane, may or may not sensitize the myocardium and increase the risk of ventricular fibrillation.[1-6] Knowledge of such interactions is important because of the widespread use of epinephrine to achieve hemostasis during surgical procedures. However, no reports have demonstrated the interaction of epinephrine with either anesthetic agent in man, nor has a comparison been made with a drug such as halothane, which is known to sensitize the heart.

Accordingly, we determined the dosage of epinephrine in saline solution required to produce premature ventricular extrasystoles (PVCs) in elective surgical patients anesthetized with halothane, enflurane, or isoflurane, and the epinephrine dosage that produced PVCs when administered in a lidocaine solution.

METHODS

Patients undergoing transphenoidal pituitary operations at our institution routinely receive nasal and oral submucosal injections of epinephrine to minimize surgical bleeding. Fifty such patients (ASA status I or II), divided into 4 groups (table) were studied. All were without evidence of significant cardiovascular disease. No premedication or IV inducing agent was given. Two groups were anesthetized with halothane, one with isoflurane, and one with enflurane. One halothane group and the enflurane and

*Assistant Clinical Professor/Anesthesia, Pharmacology.
†Professor, Anesthesia.
‡Professor and Chairman, Neurosurgery.
§University of California, San Francisco, California 94143.

This study was supported in part by USPHS 5-P01-GM 15571, NS 05593-06, and Ohio Medical Products, Division of Airco, Inc.
Paper received: 9/18/75
Accepted for publication: 1/26/76

TABLE

Patient Ages, Weights and Heights Are Listed Above the Estimates of the Dose (ED_{50}) of Epinephrine Which Produced 3 or More PVCs

	Halothane	Halothane-lidocaine	Enflurane	Isoflurane
Number of patients	10	9	15	16
Age, years	40.8 (±19.9)	39.9 (±14.7)	36.9 (±15.3)	41.9 (±12.7)
Weight, kg	80.9 (±24.4)	89.4 (±13.9)	69.2 (±16.3)	76.6 (±18.9)
Height, cm	163.0 (±15.0)	181.6 (±20.6)	162.6 (±7.0)	165.0 (±13.8)
Epinephrine ED_{50}, μg/kg	2.11 (±0.15)	3.69 (±0.42)	10.9 (±8.9)	6.72 (±0.66)

Each average number is followed by the standard deviation. The ED_{50} for halothane, halothane-lidocaine, and isoflurane differed significantly ($p<0.01$). No comparison could be made with enflurane because the slope of its dose-response curve (fig 1) did not parallel the slope for the other agents.

isoflurane groups received a freshly prepared solution of either 1:100,000; 1:150,000, or 1:200,000 epinephrine in saline solution (10, 6.7, or 5 μg/ml, respectively). The remaining halothane group received epinephrine, 1:200,000, freshly prepared in 0.5 percent lidocaine solution. After induction, the patient's trachea was intubated and ventilation was controlled to produce an arterialized venous blood-gas Pco_2 of 30 to 40 torr, measured with a standard Severinghaus electrode. Succinylcholine was used in 5 patients to assist endotracheal intubation.

During the 30 minutes usually required for positioning and preparation of the surgical site, anesthetic gas tensions, as measured by ultraviolet (halothane) or infrared (enflurane or isoflurane) analysis were adjusted to 1.25 times MAC,* and a control ECG lead with well-visualized P waves was recorded usually for 3 minutes immediately before injection. The surgeon then injected epinephrine into oral and nasal submucosal areas, as indicated by operative needs. A continuous ECG record was obtained during and for 3 to 10 minutes after termination of the injections, which required 3.5 to 11 minutes to complete. If PVCs occurred during injection, the injection was halted until the arrhythmias resolved. If frequent multifocal ventricular arrhythmias occurred, lidocaine (100 mg) was administered in a bolus and the injection was terminated.

We arbitrarily defined the appearance of 3 PVCs at any time during or immediately following epinephrine injection as indicating ventricular irritability, since an occasional single PVC may occur in the normal anesthetized patient. Patients were considered to have a positive or negative response based on this criterion; no positive responses were observed in any patient prior to injection. Positive and negative responses were plotted versus dose in μg/kg.

Data were analyzed with a UCSF† double-precision version of a quantal regression program, written by P. Clayton.‡ The significance of differences between the doses producing a positive response in 50 percent of patients (ED_{50}) was tested by Student's *t*-test, except that such testing was not done for the enflurane group because its response curve did not parallel those of the other agents.

RESULTS

Age, weight, and height (table) and $Paco_2$ did not differ significantly among the 4 groups. However, the epinephrine ED_{50} values for halothane, halothane-lidocaine, and isoflurane groups (table) differed significantly ($p<0.01$). The ED_{50} was least in patients given epinephrine in saline during halothane anesthesia (halothane group) (figs 1, 2). The ED_{50} in patients given epinephrine in 0.5 percent lidocaine (halothane-lidocaine group) was greater than that for the halothane group but less than that for the isoflurane group. The enflurane

*MAC is the alveolar concentration of anesthetic required to eliminate movement in response to an incision in 50% of patients.

†University of California at San Francisco.

‡London School of Hygiene and Tropical Medicine, April 1969.

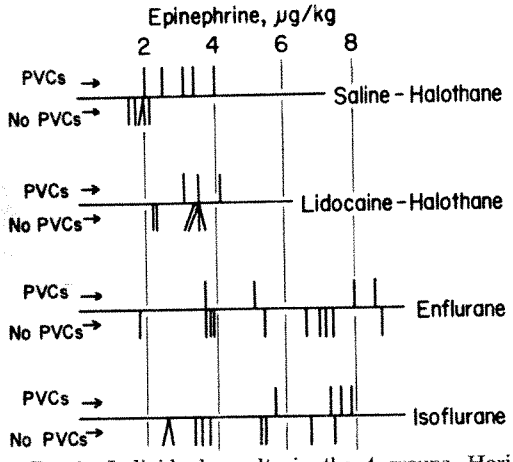


FIG 1. Individual results in the 4 groups. Horizontal lines indicate concentration of epinephrine injected submucosally. Each vertical line extending from horizontal lines represents 1 patient: an upward direction signifies that the patient experienced 3 or more PVCs; a downward deflection signifies that 2 or fewer PVCs appeared within 10 minutes after injection.

group had the highest ED_{50}, but the flatness and hence nonparallel nature of its dose-response curve made any statistical comparison invalid.

In the halothane group, 4/5 patients with arrhythmias had ventricular tachycardia. Two "negative-response" patients near the ED_{50} (1.9 and 1.8 μg/kg) had 1 PVC each. Although only PVCs were used to define ventricular irritability, other arrhythmias occurred. Heart rate increased in nearly all patients, most developing a sinus tachycardia (rate greater than 100 bpm). A nodal rhythm occurred in 8 patients: 2 in the halothane group, 1 in the halothane-lidocaine group, 3 in the enflurane group, and 2 in the isoflurane group. As might be expected, the number of PVCs correlated with the dose of epinephrine in the halothane groups. In the enflurane and isoflurane groups, although positive PVC responses were obtained, the total number of abnormal complexes were too few to permit a correlation.

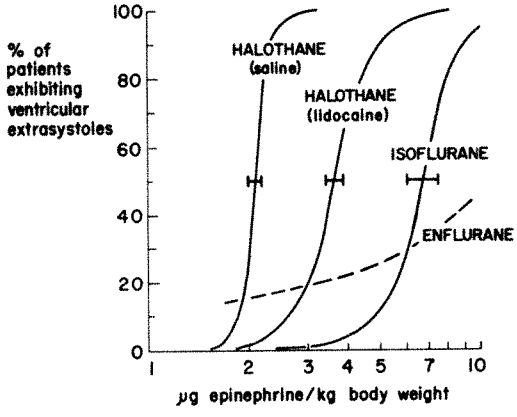


FIG 2. The results of the statistical analysis suggest that the two halothane and the isoflurane curves (but not the enflurane curve) are parallel and that the ED_{50}'s are significantly different from each other ($p<.01$). The bars indicate the standard deviation from the ED_{50}.

DISCUSSION

Approximately 3 times as much epinephrine was required to produce 3 or more PVCs during isoflurane as during halothane anesthesia, with enflurane probably comparable to isoflurane in this regard. If we assume (as suggested by the present study) that a dose equaling half the ED_{50} is unlikely to produce PVCs, then these potentially dangerous arrhythmias likely will not follow injections of up to 1 μg/kg during halothane and 3.4 μg/kg during isoflurane anesthesia. In a 70-kg patient, such doses would be produced, with halothane, by 14 ml and, with isoflurane, with 47 ml of a 1:200,000 solution of epinephrine in saline.

Furthermore, if 0.5 percent lidocaine were given concomitantly, these "maximum safe doses" probably could be increased by 50 percent. This protective effect of lidocaine was studied only with halothane. However, on the few occasions when PVCs appeared and were treated with lidocaine during isoflurane or enflurane anesthesia, the arrhythmias immediately disappeared. This would suggest that the protection offered by concomitant lidocaine also would apply to these anesthetics.

The maximum safe doses suggested above may be modified by several factors. In our study, injection was into vascular oral and nasal mucosa. Injection into less vascular subcutaneous tissues might decrease the rate of epinephrine uptake and thereby raise the maximum safe dose. Obviously, accidental intravenous injection would do the opposite. Although no ventricular arrhythmias may be induced by the maximum safe doses, transient tachycardia and hypertension may result. These cardiovascular effects may produce myocardial ischemia in patients with compromised coronary arteries.

We studied unmedicated patients whose ventilation and anesthetic dosage were comparable in all groups. We have not determined the effect of variations of these factors in man, nor are comparable data in

man available. However, studies in dogs by Joas and Stevens[4] indicated no effect or a protective effect from increases in anesthetic dose (halothane, fluroxene, isoflurane) or in $Paco_2$. Our results agree both qualitatively and quantitatively with the finding in dogs that the dose of epinephrine required to produce PVCs during isoflurane anesthesia is 4 times that required during halothane.[4,5]

In part our results agree with those of Katz and associates[7] who suggested a safe dose of epinephrine during halothane anesthesia of 1 μg/kg. We disagree with Katz's suggestion that the concomitant injection of lidocaine with epinephrine affords no increased protection from arrhythmias. However, the individual doses of epinephrine used in the Katz study were too low to evoke a significant increase in the incidence of arrhythmias; this would prevent discernment of the protective effect of lidocaine.

Halothane and enflurane or isoflurane appeared to differ in their propensity to sustain ventricular arrhythmias. When ventricular irritability appeared during halothane, it was often followed by frequent abnormal beats, leading to ventricular tachycardia. In contrast, when ventricular arrhythmias appeared with the other 2 anesthetics, the abnormal beats were occasional, intermittent, and not necessarily sustained. This impression is further supported in the case of isoflurane by 3 patients (data not included in present study) who each received 11 μg/kg of epinephrine and who failed to demonstrate any PVCs. One other patient anesthetized with enflurane was given 13 μg/kg and demonstrated a positive response (data also not included because epinephrine dosage exceeded 10 μg/kg).

While the dose-response relationships shown in figure 1 demonstrate a nonparallelism of enflurane with the other curves, precluding statistical evaluation, this should not suggest that these data are unimportant, since they can be compared clinically with other data. Our dose-response curve with enflurane may represent only the lower part of a larger dose-response curve which cannot be examined because such an examination would require unjustifiably high doses. Defining the larger part of the enflurane curve would be interesting, but would have to be done in animals, which would defeat the intent of our study.

CONCLUSIONS

Two clinical implications are suggested by our results. Catecholamine drug support often is required following cardiopulmonary bypass for cardiac surgery. If ventricular arrhythmias are of concern, enflurane or isoflurane might represent a better anesthetic choice for such patients. Finally, our results would suggest that ventricular arrhythmias would be less likely to occur in patients suffering from pheochromocytoma when these patients are anesthetized with isoflurane or enflurane rather than with halothane.

ACKNOWLEDGMENT

We appreciate the assistance provided by Dr. S. Wiley, who performed the quantal regression analyses.

REFERENCES

1. Virtue RW, Lund LO, Phelps M Jr, et al: Difluoromethyl 1, 1, 2-trifluoro-2 chloroethyl ether as an anaesthetic agent: results with dogs and a preliminary note on observations with man. Can Anaesth Soc J 13:233-241, 1966

2. McDowell SA, Holl KD, Stephen CR: Difluoromethyl 1, 1, 2-trifluoro-2-chloroethyl ether; experiments on dogs with a new inhalational anaesthetic agent. Br J Anaesth 40:511-516, 1968

3. Botty C, Brown B, Stanley V, et al: Clinical experiences with compound 347, a halogenated anesthetic agent. Anesth Analg 47:499-505, 1968

4. Joas TA, Stevens WC: Comparison of the arrhythmic doses of epinephrine during Forane, halothane and fluroxene anesthesia in dogs. Anesthesiology 35:48-53, 1971

5. Tucker WK, Rackstein AD, Munson ES: Comparison of arrhythmic doses of adrenalin, metaraminol, ephedrine and phenylephrine during isoflurane and halothane anaesthesia in dogs. Br J Anaesth 46:392-396, 1974

6. Munson ES, Tucker WK: Doses of epinephrine causing arrhythmia during enflurane, methoxyflurane and halothane anaesthesia in dogs. Can Anaesth Soc J 22:495-501, 1975

7. Katz RL, Matteo RS, Papper EM: The injection of epinephrine during general anesthesia. 2. Halothane. Anesthesiology 23:597-600, 1962

A Preplanned Treatment for Malignant Hyperpyrexia

JOHN G. FRASER, MD*
ROBERT S. CRUMRINE, MD†
ROBERT J. IZANT, JR, MD‡
Cleveland, Ohio§

Although a rare complication of general anesthesia, unanticipated malignant hyperpyrexia requires a rapid, organized treatment plan. With the aid of a treatment protocol sheet and a compact drug and cooling package, treatment can be implemented quickly in each operating room.

THE clinical entity of malignant hyperpyrexia has been discussed in numerous articles in the anesthesiology literature over the past 10 years.[1-3] The syndrome has been defined as a pharmacogenic disorder of unknown cause, occurring during general anesthesia in humans and swine and resulting in life-threatening temperature elevations. The onset of hyperpyrexia may be evident upon induction of anesthesia, heralded by paradoxically induced rigidity in response to succinylcholine; or it may suddenly occur intraoperatively in association with potent inhalation agents or in the postoperative recovery room.[4,5] Even the previously implied safety of d-tubocurarine in susceptible patients has been questioned by Britt and her associates.[6] Cases of malignant hyperpyrexia have been reported during a 2nd or 3rd anesthetic procedure following previous uneventful exposures.[7]

In the orderly and predictably scientific investigations of the hyperpyrexia syndrome in susceptible swine, several treatments have proved successful. Epidural anesthesia and the drugs triiodothyronine, dantrolene sodium, and procainamide are among the treatments that have prevented or aborted the induced hyperpyrexia in swine.[8-11] The survival of a patient with malignant hyperpyrexia through cooling by a pump-oxygenator has been reported.[12]

In the years 1973-1976, a period during which approximately 17,000 pediatric anesthetics were administered, we encountered 6 cases of malignant hyperpyrexia, all in the pediatric age groups. All but one of these cases represented a paradoxical response to succinylcholine on induction or the development of a rapidly rising fever from a normal initial temperature, rising to above 40° C within 5 minutes under halothane anesthesia. All but one patient responded successfully to a termination of anesthetic and conservative cooling efforts. The 1 death was specifically attributed to uncontrolled malignant hyperpyrexia.

Until further evidence supports an increased clinical efficacy of a specific drug, we have chosen procainamide as the principal drug in our treatment regime. We recognize that parenterally injectable dantrolene sodium offers the advantages of quite specifically acting on skeletal muscle, without a negative inotropic cardiac effect.[10] However, its successful use in the hyperpyrexia syndrome in man has not yet been

*Assistant Professor of Anesthesiology.
†Assistant Professor of Anesthesiology.
‡Professor of Pediatric Surgery and Director of Pediatric Surgery.
§Departments of Anesthesiology and Surgery, Case Western Reserve University, School of Medicine, Cleveland, Ohio 44106.

Paper received: 10/1/75
Accepted for publication: 1/12/76

adequately tested. Also, the FDA has recently warned of hepatoxocity associated with dantrolene.

The difficulties in preparing for the use of a pump-oxygenator and the slow onset of an effective epidural anesthetic make these treatment modalities unattractive as a preplanned approach to the unexpected hyperpyrexia syndrome.

In forming our treatment regime, we seek the advantages of simplicity and immediate availability. Compactly stored and clearly labeled, each operating room (OR) contains the following items:

I. "Malignant Hyperpyrexia Protocol;" laminated in transparent plastic.

II. One translucent vinyl film plastic sheet: (0.006 gauge), 140 x 122 cm in size.

III. 10-ml vial of procainamide HCl (100 mg/ml).

IV. 10-ml syringe with an 18-gauge needle.

V. 500-ml bottle of 5% dextrose in water.

VI. 1000-ml bottle of normal saline solution, kept cold in OR refrigerator.

VII. A ready source of ice and a routinely stocked emergency cart.

The following protocol sheet, written in "cookbook" form, leads the physician quickly through a rare and stressful emergency.

MALIGNANT HYPERPYREXIA PROTOCOL

A. *Recognition of the Syndrome:*

1. Hypertonus of skeletal muscle may occur.
   a. IMMEDIATE: Immediately following the administration of succinylcholine. FAILURE OF SKELETAL MUSCLE TO RELAX AFTER SUCCINYLCHOLINE IS AN INDICATION TO POSTPONE SURGERY AND REEVALUATE.
   b. DELAYED: Later in the anesthetic when using potent agents, commonly halothane.
2. Unexplained tachypnea, tachycardia, sweating, cyanosis, or overheated soda lime are nonspecific early signs.
3. An unexplained rise in body temperature (1° C).

THE SYNDROME MUST BE RECOGNIZED BEFORE THE THERMAL REACTION IS SEVERE OR WELL ESTABLISHED. A RISE IN BODY TEMPERATURE MAY BE A LATE SIGN.

B. *Therapeutic Measures:*

1. DISCONTINUE ALL INHALATIONAL AGENTS AND RELAXANTS AND DISCONTINUE THE SURGERY AS SOON AS POSSIBLE.
2. HYPERVENTILATE WITH 100% OXYGEN.
3. DRUG THERAPY MUST BE STARTED IMMEDIATELY.
   a. If the patient develops muscle rigidity administer *diluted* procainamide intravenously. This solution containing 1 gm (10 cc) of procainamide in 500 cc can be infused rapidly until the rigidity subsides and then be reduced to a slower rate or discontinued. Observation of the EKG and the blood pressure are mandatory during this potent drug therapy. Vasopressors may be indicated.
   b. Sodium bicarbonate 2 mEq/kg IV stat and repeat in accordance with blood gas measurements.
   c. Mannitol—1 gram/kg IV.
4. COMMENCE ACTIVE COOLING, IF A RISING TEMPERATURE IS ENCOUNTERED. PLACE THE PATIENT IN THE PLASTIC SHEET, APPLY ICE BAGS AND ICE WATER. INTRAGASTRIC COOLING MAY ALSO BE CONSIDERED. IF THE PERITONEAL CAVITY IS OPENED, STERILE ICE SALINE MAY BE POURED INTO THE OPENING.
5. IF BODY TEMPERATURE FAILS TO QUICKLY RECEDE WITH EXTERNAL COOLING, VASODILATORS MAY BE INDICATED. INTRAVENOUS CHLORPROMAZINE (THORAZINE) CAN ACCOMPLISH THIS DESIRED VASODILATION, BUT ONLY AFTER ADEQUATE INTRAVASCULAR FLUID VOLUME HAS BEEN ATTAINED.

6. INSERT A SECOND INTRAVENOUS CANNULA AND GIVE REFRIGERATED NORMAL SALINE SOLUTION.

C. *Investigative Measures:*

1. Monitor by: esophageal stethoscope, blood pressure cuff, electrocardiogram, thermometer (rectal, esophageal and particularly intramuscle thermistor).
2. Insert an arterial cannula for sampling blood gases and pH.
3. Take blood specimens (10 ml) immediately and measure: electrolytes (Na, K, Cl, Ca, Po_4, and Mg), creatine phosphokinase (CPK), SGOT and LDH, and correct excesses and deficits in electrolytes. Repeat electrolyte determinations at frequent intervals.
4. Repeat the arterial blood measurements at 10-minute intervals and correct on the basis of the results.
5. Catheterize and take urine sample for hemoglobin and myoglobin estimation.
6. Measure urine output.
7. Anticipate massive disseminated intravascular coagulopathy. Draw blood for essential clotting factors; especially platelets, fibrinogen, prothrombin, factors V, VII, VIII, X, and calcium. If the diagnosis of DIC is made, administer heparin 250 mg/24 hours by continuous IV drip.

The admonitions in item C-7, on intravascular coagulopathy and its therapy are based on studies by Daniel's group[13] and Nemerson.[14]

The heavy gauge plastic sheet is rapidly unfolded under the patient and hung on IV poles to form an "instant bathtub" (figure). The sheet, even when filled with ice and water, allows clear access to the patient's head, airway, and extremities and allows adequate monitoring of vital signs and access to peripheral veins and arteries; the conventional bathtub permits none of these advantages. Additional IV routes for infusion of refrigerated normal saline solution are more easily established and arterial blood sampling is more easily obtained.

The 10-ml vial of procainamide (10%

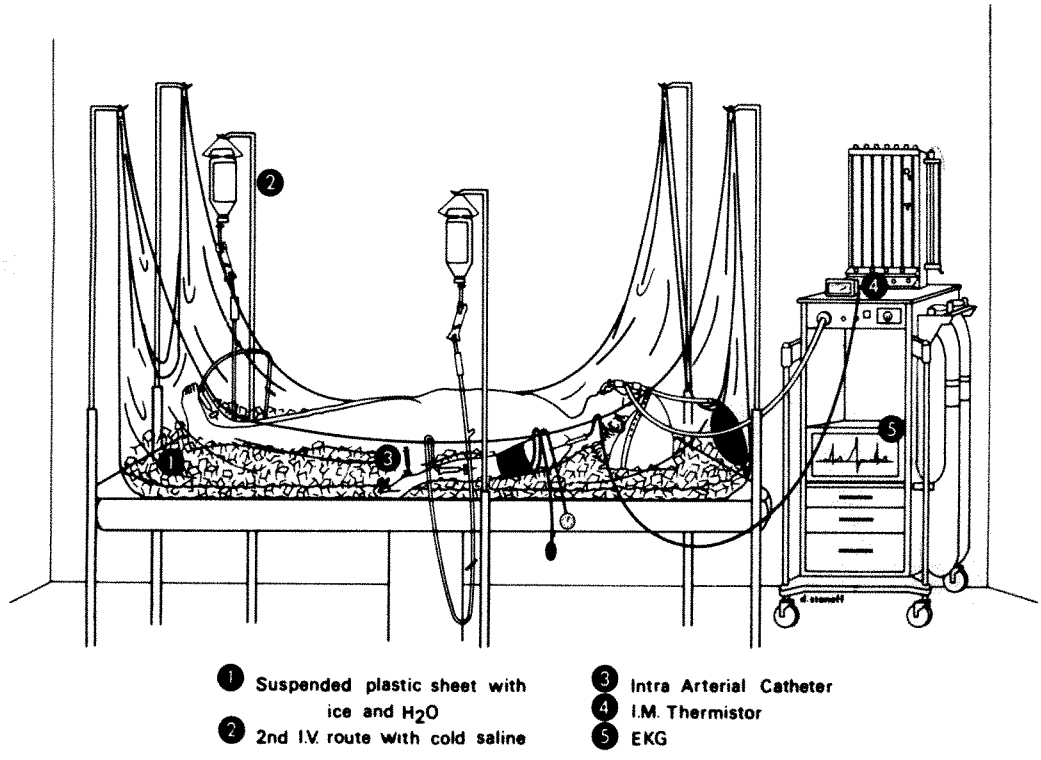


FIGURE. Active malignant hyperpyrexia treatment.

solution) when added to the 500 ml of diluent is a good concentration to be administered IV until the patient's rigor subsides.[11] Procainamide remains pharmacologically active at ordinary OR temperatures (under 29.4° C) for 2 years and then should be discarded.*

ACKNOWLEDGMENT

Certain sections of our Protocol Sheet were extracted from a teaching form used in The Hospital for Sick Children, Toronto, Canada. This was supplied by their Director of Anaesthesia, D. J. Steward, MD.

*Personal communication, ER Squibb & Sons, Princeton, New Jersey.

REFERENCES

1. Relton JES, Creighton RE, Johnston AE, et al: Hyperpyrexia in association with general anaesthesia in children. Can Anaesth Soc J 13:419-424, 1966

2. Thut WH, Davenport HT: Hyperpyrexia associated with succinylcholine-induced muscle rigidity: a case report. Can Anaesth Soc J 13:425-428, 1966

3. Wilson RD, Dent TE, Traber DL, et al: Malignant hyperpyrexia with anesthesia. JAMA 202:183-186, 1967

4. Britt BA: Recent advances in malignant hyperthermia. Anesth Analg 51:841-850, 1972

5. Schweizer O, Howland WS, Ryan GM, et al: Hyperpyrexia in the operative and immediate postoperative period. Anesth Analg 50:906-914, 1971

6. Britt BA, Webb GE, LeDuc C: Malignant hyperthermia induced by curare. Can Anaesth Soc J 21:371-375, 1974

7. Halevy S: Hyperthermia during a second anesthetic. Anesthesiology 35:444-445, 1971

8. Kerr DD, Wingard DW, Gatz EE: Prevention of porcine malignant hyperthermia by epidural block. Anesthesiology 42:307-311, 1974

9. Lister D: Correction of adverse response to suxamethonium of susceptible pigs. Br J Med 1: 208-210, 1973

10. Harrison G: Control of the malignant hyperpryrexia syndrome in MHS swine by dantrolene sodium. Br J Med 47:62-65, 1975

11. Strobel GE: Treatment of anaesthetic-induced malignant hyperpyrexia. Lancet 1:40, 1971

12. Ryan J, Donlan JV, Malt RA, et al: Cardiopulmonary bypass in the treatment of malignant hyperthermia. N Engl J Med 290:1121-1122, 1974

13. Daniels JC, Polayes IM, Villar R, et al: Malignant hyperthermia with disseminated intravascular coagulation during general anesthesia: a case report. Anesth Analg 48:877-883, 1969

14. Nemerson Y: Generalized bleeding associated with diffuse intravascular coagulation. Conn Med 32:40-44, 1968

BLOOD CULTURES. Results of blood cultures drawn via intravascular venous or arterial catheters were compared with findings from simultaneously obtained samples via percutaneous venipuncture. Results were identical in 161 of 174 comparisons (92 percent). Staphylococcus epidermidis was more likely to be present in catheter obtained samples. It appears that blood cultures obtained from catheters are as reliable as venipuncture samples. The ease and lack of trauma in obtaining blood samples from indwelling catheters are additional advantages. *(Tonnesen A, Peuler M, Lockwood WR: Cultures of blood drawn by catheters vs venipuncture. JAMA 235:187, 1976)*

Editors share the belief that medical writing is capable of vast improvement. This article is one of a series of personal communications from Charles G. Roland, M.D., former Senior Editor of JAMA, to John T. Martin, M.D., Associate Editor of Anesthesia & Analgesia . . . Current Researches. Dr. Roland is Chairman, Department of Biomedical Communications, Mayo Clinic, Rochester, Minnesota 55901.

Thoughts About Medical Writing

XXXVII. Verify Your References

Dear Tom:

Who was killed in 1938 and never had a mother? Don't you even want to guess? All right, it was O. Uplavici, the much-cited author of an important paper, published in 1887, on amebic dysentery. This paper first described the experimental transmission of amebic dysentery from man to the cat.

Why should any anesthesiologist be interested in this tale of infectious diarrhea? Because of the riddle I began with, and because I am writing today about verifying references. O. Uplavici was killed by the pen of Clifford Dobell, in 1938, and he had no mother—or father—because he never existed. The story is a classic of bibliographic error.

Jaroslav Hlava, of Prague, wrote an article on dysentery and published it in a Czech medical journal in 1887. Being a Czech, and writing in Czech, he understandably gave his title, "On Dysentery," in Czech also—"O. Uplavici." A German writer prepared a German-language abstract and, unaccountably, dropped Hlava's name and cited O. Uplavici as the author. The error was compounded in many interesting ways until finally exposed by Dobell.[1]

Similar, though less spectacular, errors occur often. Few studies seem to have been made of this phenomenon, but two recent ones perhaps deserve comment. In one, in which every reference in every paper accepted by a national journal for an entire year was checked, almost two-thirds of these 1,867 references were incorrect in some feature or were unverifiable.[2] And in another study, the error rates in references published in 10 major journals ranged from 13% to 50%.[3]

Does this really matter? Surely it ought to. References are supposed to be guides to the reader, indicating where the author derived data or ideas. And some readers do look up references, sometimes. If the citations are wrong, the reader may have difficulty finding what he or she wants, or may be unable to find it. Perhaps even more important is a philosophical-ethical issue: the published article is the culmination of an author's work. It should be error-free, for who can have confidence in a work in which he can find mistakes, whether in the data, the interpretations, or the references?

So verifying references is no mere exercise in pedantry. Yet obviously, it is something that few authors do—or do properly.

Most errors are simple enough to explain. Page 196 becomes 169. "Mar." becomes "May." "Ann Int Med" becomes "Arch Int Med." Little slips, typical of hurrying humanity. We all make this kind of error when we transcribe information. The sin occurs in passing understandable carelessness off as information.

The problem is universal. There is no cure except careful checking of the accuracy of every citation, late in the writing process

but well before the final typing stage. This checking must include every element of the citation. The author of the reference wants his name spelled correctly; moreover, ensuring that it is correct helps your reader and may prevent severe indigestion on the part of the computers that are now increasingly used to record, sort, and retrieve scientific information. Similarly, the title of the cited article must be given exactly as it appeared in the original publication; do not abbreviate in any way. The journal title must be precise, as well as the volume number, pagination, and date published.

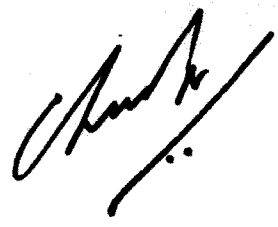
Most journals provide specific instructions about the way they want this data to be presented—their "style"—and you should try to follow their rules. If you have difficulty doing so, I advise that you send the complete reference—full journal title spelled out, for example—and let the journal convert it to their format. Unfortunately, minute differences in format exist between one journal and another, although most of the major clinical journals on this continent have agreed on a standard reference style. (For examples, see any article in this issue.)

A common reason for errors in reference citations probably is the frequency with which an untrained and uninstructed person is made responsible for checking the citations. All too often, a secretary or a clerk is sent off to the library with few or no directions except to "check the references." But a little training quickly cures this problem.

Indeed, of all the problems of medical writing, that of publishing incorrect references must be the easiest to solve. The solution requires only increased attention to a routine—and therefore often neglected—chore. Place[4] presented the matter succinctly just 60 years ago:

> Take no reference for granted. Verify the reference that your best friend gives you. Verify the reference that your revered chief gives you. Verify, most of all, the reference that you yourself found and jotted down. To err is human, to verify is necessary.

Best regards,



[Charles G. Roland, M.D.]

REFERENCES

1. Dobell C: Dr. O. Uplavici (1887-1938). Parasitology 30:239-241, 1938

2. Key JD, Roland CG: Accuracy of references in articles accepted for publication in the Archives of Physical Medicine and Rehabilitation (submitted for publication)

3. Goodrich JE, Roland CG: Accuracy of published medical reference citations. J Tech Writing Commun (in press)

4. Place F Jr: Verify your references: a word to medical writers. NY Med J 104:697-699, 1916

Maintenance of Body Temperature by Heated Humidification

HENRY C. TAUSK, MD*
RAYMOND MILLER, MD†
ROBERT B. ROBERTS, MD‡
New York, New York

Though difficult to prove conclusively, humidification of anesthetic gases during prolonged surgery appears beneficial. Even slight falls in body temperature are detrimental, causing significant increases in O_2 consumption in the immediate postoperative period. A new heated humidifier which supplies gases at 100% relative humidity at 35° C at the patient inlet has been used both to supply humidity and to prevent a fall in interoperative temperature. This was successfully employed in 19/25 prolonged procedures. The warmed humidified gases contributed significantly to the maintenance of homeostasis during anesthesia.

ADEQUATE humidification of the patient's tracheobronchial tree and the maintenance of normal body temperature are of paramount importance during prolonged surgical procedures.

The comfort of the surgical team necessitates cool air-conditioned operating rooms,[1] which may result in a decline in the patient's body temperature. Many methods have been used to maintain or raise body temperature, including thermal blankets[2] or garments,[3] warm IV fluids,[4] radiated heat, and heat exchangers.[5] These methods, while often effective, have the disadvantages of not being universally applicable. Thermal blankets and garments may still leave large areas of the body exposed, are difficult to use in such positions as knee-chest, and may cause skin burns.[6] Extracorporeal circulation incorporating a heat exchanger is expensive, complicated, and not always readily available.[5]

The importance of humidification during prolonged anesthesia has long been recognized; exposure to dry inhaled gases for over 1 hour produces damage to the epithelium of the respiratory tract.[7] Different means of humidification have been recommended but many fail to provide optimal humidity, since the relative humidity of gases delivered at room temperature falls when the gases attain body temperature. Satisfactory humidifiers are often adaptations of equipment used in respiratory therapy and, while eminently suitable during controlled ventilation, provide an unacceptable resistance to inhalation for the patient during spontaneous ventilation and therefore must be modified.[8]

Present Study.—A prototype of a new concept in humidifiers that provides heated humidified anesthetic gases to the patient without increased resistance during spontaneous ventilation, and in which gas temperature can be fairly rapidly adjusted, was used to investigate the efficacy of heated inspiratory gases in the maintenance of normothermia during prolonged anesthesia.

The humidifier* (fig 1, 2) consists of a simple reservoir containing a rotating brush whose fibers pass through heated water covering the lower half of the brush and then flick past a baffle above the water level, producing a fine spray of water droplets. The water is heated through a metal backplate that transmits heat directly from the

*Prototype (Patent #3,345,047) was manufactured by M. G. Humidifiers, Inc., Ocean, New Jersey.

*Assistant Clinical Professor of Anesthesiology.
†Associate Clinical Professor of Anesthesiology.
‡Professor of Anesthesiology.
Mount Sinai School of Medicine of the City University of New York, New York, New York 10029.

Paper received: 7/7/75
Accepted for publication: 2/17/76

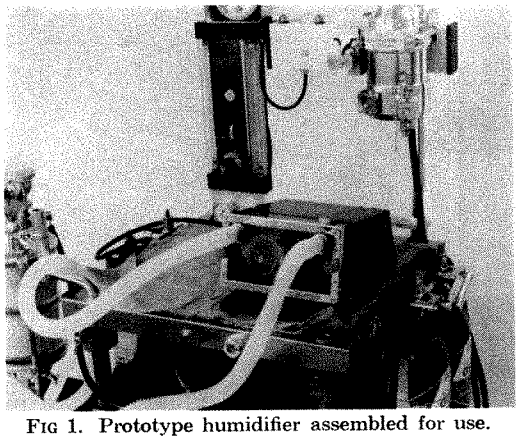


FIG 1. Prototype humidifier assembled for use.

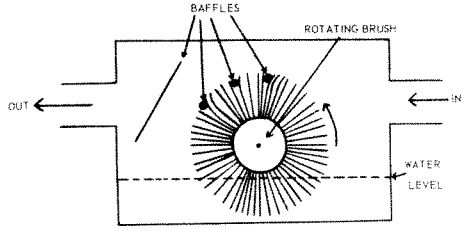


FIG 2. Diagramatic representation of humidifier. Heat both from the motor and an auxiliary rheostat-controlled heating bar is transmitted via the backplate to the water.

motor and also from an auxiliary rheostat-controlled heater which is turned on when more rapid heating of the water is required. While this is a prototype and is not approved for use with flammable anesthetic agents, it is anticipated that the production device will be so constructed as to meet Underwriter's Laboratories requirements for safe use in a hazardous atmosphere.

The high humidity over a wide range of temperatures safeguards against any static electricity problems. Gases from the anesthetic machine travel through the spray of water droplets and are thus exposed to a large water surface area, rapidly becoming heated and humidified. A further baffle close to the exit port causes most of the larger water particles to fall back into the reservoir.

When temperature was measured in the reservoir and at the Y-piece of a standard 101-cm polyethylene anesthetic circuit, a fall of approximately 10° C was found between the humidifier and the Y-piece. Relative humidity (RH) measured* at the Y-piece at 43, 36, and 22° C was 100 percent in all instances.

*Psychrometer, Taylor Instrument Company, Asheville, North Carolina.

The operating room temperature was kept between 20 and 21° C and the temperature at the inlet of the endotracheal tube was kept at approximately 35° C by manual control of the resistor controlling the humidifier heater.

Twenty-five patients, 24 of whom were undergoing neurosurgical procedures, were studied. Of these, 11 patients undergoing craniotomies had their heads draped but instrument stands over the operating table prevented their bodies from being directly covered; 4 patients underwent lumbar laminectomies and were almost completely covered by drapes; 9 patients were operated on in the sitting position and were wrapped in a Gardner antigravity ("G") suit. Though this latter might be considered to provide thermal insulation, our previous experience[3] indicated that its use might limit but not prevent the development of hypothermia. In 8 patients, induced hypotension achieved either by high concentrations of halothane or by trimethaphan infusion was an integral part of the procedure.

Patient ages ranged between 12 and 63 (mean 45) years; 12 were male and 13 female. Operating time ranged from 3½ to 15½ hours, with a mean of just under 9 hours. Inhalation anesthesia using controlled ventilation with halothane-N_2O-O_2 and muscle relaxants as necessary was used in all cases.

Patient temperature was monitored by tympanic (Arbrook Company), esophageal and rectal (Yellow Springs Instrument Company) routes and estimated to the nearest 0.2° C. Only tympanic temperature was monitored in 7 cases, while in the others tympanic plus either esophageal or rectal probes were used.

Four patients served as their own controls, body temperature being monitored throughout but the heated humidifier being introduced only after 2 to 3 hours of operation, after body temperature had already fallen.

RESULTS

All patients were normothermic at the start of anesthesia. After induction and preparation, the mean temperature was 35.7 ± 0.6° C. Fourteen patients (56%) showed an increase in temperature during the procedure, ranging from 0.5 to 2° C (mean 0.6 ± 0.3° C) (table). Five patients (20%) maintained a steady body temperature apart from minor oscillations of less than 0.4° C.

TABLE
Summary of Temperature Changes in 25 Patients Receiving Heated Humidified Anesthetic Gases

	Normotension	Induced hypotension	Total
Temperature ↑	11 (65%)	3 (38%)	14 (56%)
Temperature steady	4 (23%)	1 (12%)	5 (20%)
Temperature ↓	2 (12%)	4 (50%)	6 (24%)

Six patients (24%) showed a decline of between 0.5 and 1.1° C despite the warmed humidification, and additional means of warming was necessary to prevent a further fall in temperature. Warming was achieved by use of a thermal blanket.

Of the 6 cases showing a decline in body temperature, 4 were undergoing induced hypotension with high concentrations of halothane. Considering the 8 patients undergoing induced hypotension, 4 showed a decline in temperature and 3 an increase in temperature.

Of the 4 cases where temperature fell before warmed humidification was introduced, 2 showed a final increase in temperature and in the other 2, the temperature returned to the preoperative level.

All cases are summarized in figure 3.

CASE REPORTS

Case 1.—A 58-year-old woman underwent removal of a posterior fossa tumor in the sitting position. A left tympanic and an esophageal thermal probe were inserted and demonstrated a slight but constant discrepancy, the tympanic probe indicating a temperature of approximately 0.4° C lower than the esophageal probe. During the first 2 hours of anesthesia, a fall of 0.3° C/hr in body temperature occurred (fig 4). This downward trend was reversed when heated humidification was introduced into the anesthetic circuit and an increase in body temperature of almost 0.3° C/hr occurred over the next 4 hours. At the end of 6 hours of anesthesia (the end of operation) the body temperature was approximately 0.5° C higher than the initial temperature.

Case 2.—A 51-year-old woman underwent a craniotomy in the supine position for a pituitary tumor. Tympanic and esophageal probes showed almost identical readings. Heated humidification was used throughout the procedure. From 1120 to 1300 hr, her temperature rose approximately 0.5° C and

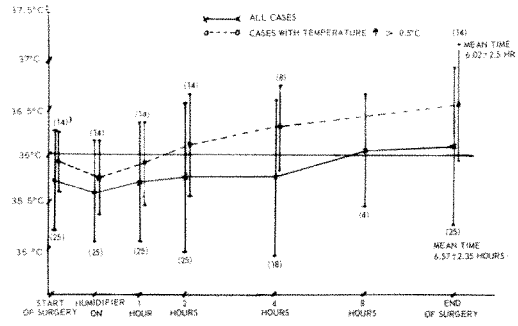


FIG. 3. Mean tympanic temperatures (±SD) related to humidifier time.

then remained constant for 1 hour (fig 5). At 1400 hr, hypotension was induced with halothane, maintaining a systolic pressure of 70 torr for 1 hour, during which time her temperature fell approximately 0.4° C. Normotension was restored at 1500 hr, following which her temperature again gradually rose.

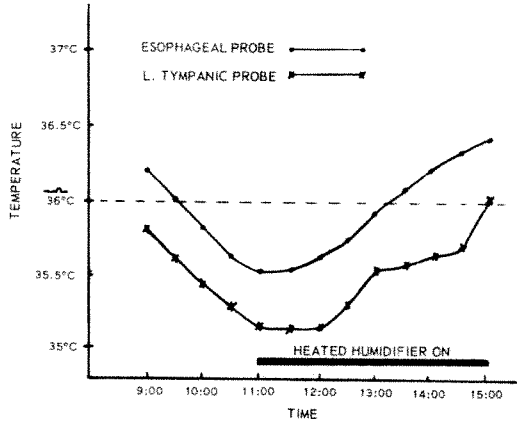


FIG 4. Temperature chart of a 58-year-old woman (case 1) undergoing removal of posterior fossa tumor.

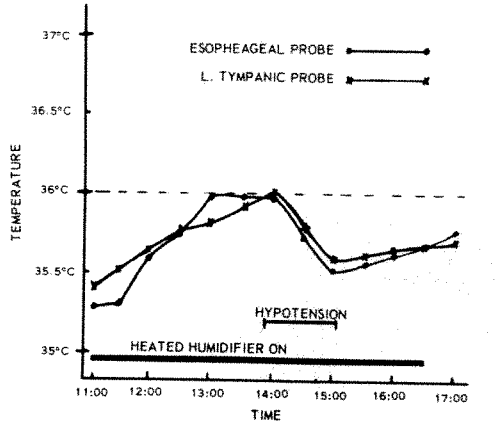


FIG. 5. Temperature chart of a 51-year-old woman (case 2) undergoing craniotomy for pituitary tumor.

No complications in any way referable to the heated humidification occurred in the postoperative period in any patient.

DISCUSSION

The value of humidification of anesthetic gases is still unclear despite the cytologic work of Chalon and colleagues,[7] who have conclusively demonstrated changes in tracheobronchial cells after 1 hour of dry gas anesthesia, although a recent statistically controlled series[9] failed to show any difference in the incidence of postoperative complications. However, a reduction in the incidence of cell decay after 3 hours of anesthesia from 45 percent with dry gases to 1 percent with adequate humidification,[10] the reduction in crusting, and the maintenance of ciliary movement are cogent arguments in favor of humidification.

Excessive addition of water to the tracheobronchial tree may produce harmful effects, including atelectasis and positive water balance, as reported with the use of ultrasonic humidifiers.[11,12] Dery,[13] while agreeing that dry anesthetic gases may be harmful, suggests that the use of a semiclosed circuit with a soda-lime absorber rather than a nonrebreathing circuit provides enough water for adequate humidification.

The prevention of hypothermia during operation is universally agreed to be desirable and the harmful consequences of even moderate falls in temperature are well documented.[14,15] Complications in the early postoperative phase, including cyanosis, respiratory distress, and hypotension, occur more frequently in patients whose body temperature has fallen. Roe and colleagues[14] showed that postoperative O_2 consumption more than doubled when the fall in temperature was between 0.3 and 1.2° C. The increase in O_2 consumption was less than 5 percent in patients whose temperatures did not fall. If the fall was over 1.3° C, the increase in O_2 consumption averaged approximately 40 percent.

Lunn[15] has pointed out the dangers of hypothermia in patients with arterial insufficiency where further vasoconstriction may occur, the almost complete absence of deep vein thrombosis as a complication of surgical procedures in warm operating rooms, and also the danger of vasodilation when the patient's temperature is restored in the recovery room, suddenly exposing an inadequate blood volume. Rashad and Benson[16] pointed out the dangers of prolongation of the effect of depolarizing muscle relaxants and too deep a level of anesthesia, due to low basal metabolism lowering anesthetic requirements.

Commonly, body temperature falls during anesthesia unless the operating room temperature is kept above 21° C. Morris[17] found that 30 percent of his patients' temperatures fell even if the room was kept between 21 and 24° C. Goldberg and Roe[18] reported that 78 percent of their patients showed a fall in temperature; the mean fall was 1.15° C during a 3-to-4-hour procedure. They calculated the average heat loss as 43.5 cal/sq m/hr.

Newman[4] used a warming blanket plus warm IV fluids for patients undergoing vascular surgery. Unwarmed patients aged 50 to 60 in his series, which had a mean operating time of 5½ hours, had a mean fall in temperature of 3.3° C. In those patients who were warmed, the mean temperature rose 0.3° C.

Most investigators report that temperature falls vary directly with the duration of the operative procedure, increased age, intrabody cavity procedures, and the use of air conditioning in the operating room. An association between the magnitude of temperature fall and anesthetic agents has not been conclusive; cutaneous vasodilation and the loss of muscular activity are the main mechanisms of intraoperative temperature fall.

Heated inhalation gases delivered at 30° C and RH 100 percent have been used for temperature control in pediatric surgery.[16] In cases of accidental hypothermia in adults,[19] a Waters canister with added CO_2 was used to produce heat and humidification. That heated humidification can increase body temperature was dramatically shown by the reported occurrence of hyperthermia while using the Emerson postoperative ventilator.[20]

As far back as 1945, experimental investigation showed that if heat is to be applied to the air passages, careful monitoring of airway temperature is mandatory.[21] An inspired gas temperature of up to 41° C is said by Miller[22] to be safely tolerated by the patient. Temperatures above this may cause tracheobronchial edema, as illustrated by a patient inadvertently given heated gases at 43.3° C.[23] Our own study has convinced us that use of a warming humidifier, such as described in the present report, offers distinct advantages, especially during prolonged surgical procedures.

REFERENCES

1. Wyon DP, Lidwell OM, Williams RGO: Thermal comfort during surgical operations. J Hyg (Camb) 66:229-248, 1968

2. Morris RH, Kumar A: The effect of warming blankets on maintenance of body temperature of the anesthetized paralyzed adult patient. Anesthesiology 36:408-411, 1972

3. Goldblat A, Miller R: Prevention of incidental hypothermia in neurosurgical patients. Anesth Analg 51:536-543, 1972

4. Newman BJ: Control of accidental hypothermia. Anaesthesia 26:177-187, 1971

5. Kugelberg J, Schuller H, Berg B, et al: Treatment of accidental hypothermia. Scand J Thorac Cardiovasc Surg 1:142-146, 1967

6. Crino MH, Nagel EL: Thermal burns caused by warming blankets in the operating room. Anesthesiology 29:149-150, 1968

7. Chalon J, Loew DAY, Malabranche J: Effects of dry anesthetic gases on tracheobronchial ciliated epithelium. Anesthesiology 37:338-343, 1972

8. Weeks DB, Broman KE: A method of quantitating humidity in the anesthetic circuit by temperature control: semiclosed circuit. Anesth Analg 49:292-296, 1970

9. Knudson J, Lomholt N, Wisberg K: Postoperative pulmonary complications using dry and humidified anaesthetic gases. Br J Anaesth 45: 363-368, 1973

10. Tayyab MA, Ambiavagar M, Chalon J: Water nebulization in a non-rebreathing system during anaesthesia. Can Anaesth Soc J 20:728-735, 1973

11. Modell JH, Diammona ST, Davis JH: Effect of chronic exposure to ultrasonic aerosols on the lung. Anesthesiology 28:680-688, 1967

12. Herzog P, Norlander OP, Engstrom CG: Ultrasonic generation of aerosol for the humidification of inspired gas during volume-controlled ventilation. Acta Anaesthesiol Scand 8:79-95, 1964

13. Dery R: The evolution of heat and moisture in the respiratory tract during anaesthesia with a non-rebreathing system. Can Anaesth Soc J 20:296-309, 1973

14. Roe CF, Goldberg MD, Blair CS, et al: The influence of body temperature on early post-operative oxygen consumption. Surgery 60:85-92, 1966

15. Lunn HF: Observations on heat gain and loss in surgery. Guys Hosp Rep 118:117-127, 1969

16. Rashad KF, Benson DW: Role of humidity in prevention of hypothermia in infants and children. Anesth Analg 46:712-718, 1967

17. Morris RH: Operating room temperature and the anesthetized paralyzed patient. Arch Surg 102: 95-97, 1971

18. Goldberg MJ, Roe CF: Temperature changes during anesthesia and operations. Arch Surg 93:365-369, 1966

19. Lloyd EL: Accidental hypothermia treated by central rewarming through the airway. Br J Anaesth 45:41-47, 1973

20. Kirch TJ, DeKornfeld TJ: Unexpected complication (hyperthermia) while using the Emerson postoperative ventilator. Anesthesiology 28:1106-1107, 1967

21. Moritz AR, Henriques FC, McLean R: The effects of inhaled heat on the air passages and lungs. Am J Pathol 21:311-331, 1945

22. Miller WF: Safety of heated humidity. Respiratory Care 19:508-512, 1974

23. Klein EF, Graves SA: "Hot pot" tracheitis. Chest 65:225-226, 1974

CARDIAC ENZYMES. The enzyme tests most commonly used for the diagnosis of myocardial infarction (SGOT, LDH and CPK) are not specific for the myocardium. However, the MB isoenzyme of creatine kinase is specific for the myocardium. The authors measured total serum enzymes and the MB isoenzyme in patients with suspected acute myocardial infarction as well as in postoperative surgical patients. In patients with myocardial infarction the magnitude of the MB isoenzyme rise was 2 to 3 times greater than that of any other enzyme. The isoenzyme did not increase in postoperative patients which contrasts with the expected rise in SGOT, LDH and CPK after any major surgical procedure. *(Smith AF, Radford D, Wong CP et al: Creatine kinase MB isoenzyme studies in diagnosis of myocardial infarction. Brit Ht J 38:225-232, 1976)*

A Comparison of the Efficiency of Three Anesthesia Circle Systems

MARILYN HARPER, MD*
EDMOND I. EGER, II, MD†
San Francisco, California‡

Three commonly employed anesthesia circle systems were tested to determine what effect the placement of the inflow port, overflow valve, and inspiratory and expiratory valves, as well as inflow rate, had on the rate of rise of anesthetizing alveolar concentrations of halothane. System efficiency was evaluated on the basis of whether alveolar gases, containing low concentrations of halothane, or fresh and dead-space gases, containing higher concentrations of halothane, were eliminated through the overflow valve. Small potentially significant differences in efficiency were found: greatest efficiency (greatest ejection of alveolar gas) occurred when inspiratory and expiratory valves were close to the endotracheal tube and the overflow valve was immediately distal to the expiratory valve. Increasing inflow rate from 1 to 3 L/min had a large impact on the rate of rise of alveolar halothane concentration. A further increase to 5 L/min had a relatively small effect.

DESPITE its widespread use, the effect of the anesthesia circuit on the development of inspired and alveolar anesthetic concentrations has not been well studied. We previously[1] measured the rate of rise of N_2O during marked hyperventilation considered sufficient to cause equality of inspired and alveolar concentrations. The rate at which the N_2O concentration rose was a function of inflow rate, system volume, and the concentration delivered (concentration effect).[2] We are not aware of any report of a similar study at normal ventilation with N_2O or, more importantly, with a moderately or highly soluble agent.

Theoretic considerations would suggest that the insertion of an anesthetic circuit between inflow and patient may hinder the development of an anesthetizing alveolar anesthetic partial pressure.[3] The circuit contains a volume which must be washed out in order to develop an inspired partial pressure, and hence that volume and the inflow rate both are determinants of the alveolar rate of rise. Furthermore, the inflow rate is important, since it also controls the amount of rebreathing. Rebreathing is of particular importance with more soluble agents, since the alveolar concentrations of such agents will be well below those delivered in the inflow.

Finally, we have suggested from both theoretic calculations[4] and mechanical models[5] that particular arrangements of anesthetic circuits are more efficient, in that some arrangements preferentially eliminate alveolar gas. Less efficient circuits do not distinguish between alveolar and fresh inflowing or dead-space gases, all three being subject to concomitant elimination.

Our recent examination of the above issues in surgical patients ventilated to normal CO_2 levels has given results in agreement with earlier predictions concerning the

*Assistant Professor.
†Professor.
‡Department of Anesthesia, University of California, San Francisco, California 94143.
This study was supported in part by USPHS 5P01 GM15571 and by a grant from the Illinois Tool Works.
Paper received: 11/3/75
Accepted for publication: 1/20/76

importance of inflow rate. We find that system arrangement has little impact on the development of the inspired and alveolar anesthetic concentration, but choice of one arrangement as opposed to another may result in significant conservation of fresh gas and hence a reduction in cost.

METHODS

Thirty-seven healthy (ASA I or II) adult patients who were to undergo elective surgery were selected for study if (1) they agreed to participate; (2) they weighed between 55 and 85 kg, and (3) there was no contraindication to the use of halothane. Premedication consisted of atropine plus barbiturate or diazepam in doses selected by the attending anesthesiologist. Induction was achieved with thiopental and endotracheal intubation facilitated with pancuronium. Ventilation was controlled at a rate of about 10/min and a volume of 10 ml/kg body weight. This ventilatory pattern produced average arterialized venous P_{CO_2} values between 32.7 and 44.4 torr (average for each group), as described below. Nasopharyngeal temperature was measured with either a mercury thermometer or Yellow Springs temperature probe. Average temperatures ranged betwen 35.4 and 36.3° C.

The arrangement of the 3 anesthetic systems selected for study is shown in figure 1. System A (Foregger) has the inspiratory and expiratory valves near the CO_2 absorber, with the inflow between the inspiratory valve and the patient. The overflow (pop-off) is between expiratory valve and absorber. System C (Ohio Medical Products) differs from system A only in that the inflow is between the absorber and the inspiratory valve. System H (Anesthesia Associates) has the inspiratory and expiratory valves placed close to the patient, with the inflow between the absorber and the inspiratory valve. The overflow is between the expiratory valve and absorber and is immediately adjacent to the expiratory valve.

Either a 1, 3, or 5 L/min O_2 inflow rate was chosen and maintained throughout the 60 minutes of study in each patient. Systems A and C were tested at all inflow rates, whereas system H only was tested at the 3 L/min inflow rate. Oxygen was delivered from a flowmeter, previously calibrated against a Collins spirometer. Halothane was added from a temperature-compensated vaporizer (Fluomatic®) at a constant predetermined concentration which, on the average, produced an alveolar concentration close to MAC.[6]

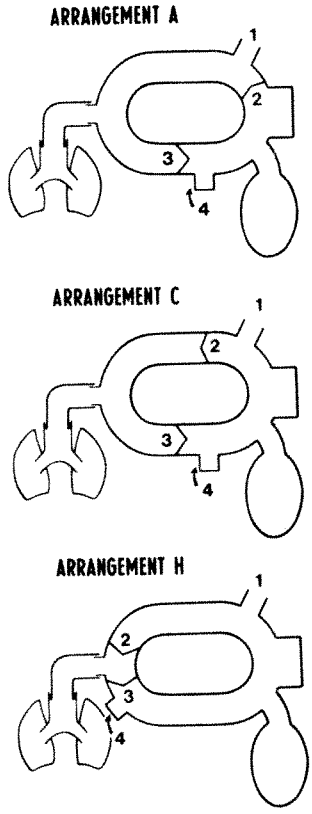


FIG 1. The 3 anesthetic arrangements (systems) described in the text. Numbers indicate system parts: 1 = inflow; 2 = inspiratory valve; 3 = expiratory valve; 4 = overflow (pop-off) valve.

End-tidal, inspired, overflow, and inflow halothane concentrations were measured at 1, 2, 4, 6, 8, and 10 minutes after the start of halothane delivery and every 10 minutes thereafter for a total of 60 minutes. Halothane concentrations were determined with an ultraviolet analyzer, calibrated every 5 to 10 minutes against an internal optical standard. End-tidal samples were taken from a nylon catheter which extended to the tracheal end of the endotracheal tube.

From the halothane concentrations obtained as indicated above, 3 ratios were determined. The first relates the inflowing concentration (F_{INF}) to the inspired concentration (F_I) and defines how rapidly the inspired concentration approaches that delivered. The second relates the alveolar (end-tidal) concentration (F_A) to F_{INF} and defines how rapidly the alveolar concentration approaches that delivered.

The 3rd ratio is the difference between

TABLE 1
Mean Age, Weight, Body Temperature, End-Tidal P_{CO_2}, and Arterialized P_{CO_2} by Groups

System	Flow, L/min	Number of subjects	Age	Weight, kg	Temperature, °C	$P_{E_{CO_2}}$	P_{CO_2}
A	1	5	35 ± 6.5	60.4 ± 3.5	36.3 ± 0.2	32.7 ± 0.9	37.8 ± 1.3
	3	5	41 ± 7.1	67.8 ± 5.4	36.3 ± 0.3	31.4 ± 1.8	35.6 ± 0.1
	5	5	45 ± 9.3	76.0 ± 4.5	35.4 ± 0.2	28.2 ± 0.5	32.7 ± 0.6
C	1	4	43 ± 9.2	64.0 ± 3.3	36.0 ± 0.2	39.9 ± 2.2	44.4 ± 2.7
	3	6	36 ± 5.3	66.8 ± 4.4	36.1 ± 0.2	34.7 ± 1.2	34.2 ± 1.2
	5	5	47 ± 2.9	66.4 ± 1.8	36.1 ± 0.1	31.0 ± 2.1	37.4 ± 1.2
H	3	7	49 ± 5.9	77.4 ± 3.0	35.9 ± 0.1	32.0 ± 2.2	40.9 ± 2.7

the pop-off (F_{PO}) and alveolar concentrations divided by the difference between alveolar and inspired concentrations; this defines the proportion of the gases popped-off which contain alveolar as opposed to inspired gas: a smaller ratio indicates a relatively greater contribution of alveolar gas. A value of zero would indicate that the popped-off gases consisted entirely of alveolar gas; a value of 1 would indicate that the popped-off gas concentration equalled the inspired concentration.

An arterialized venous blood sample was drawn at about 30 minutes and analyzed for CO_2, pH, and O_2 with electrodes and corrected for body temperature. Samples were not accepted if the P_{VO_2} did not indicate a saturation exceeding 90 percent. At the same time, we obtained an end-tidal sample for CO_2 analysis (infrared).

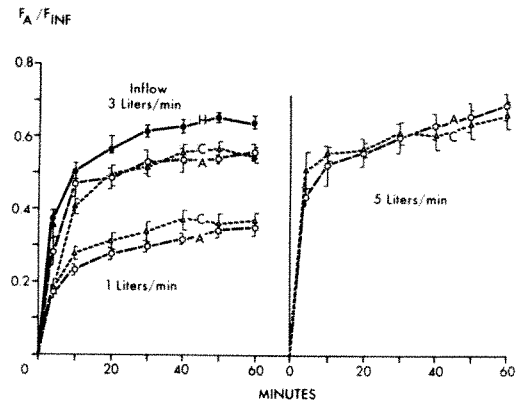


FIG 2. The rate of rise of alveolar concentration toward inflow concentration (F_A/F_{INF}) increases with higher flow rates. Low flow rates (1 L/min) prevent development of high alveolar concentrations for 1 hour, while there are only small differences between 3 L/min and 5 L/min after 20 minutes. There are no differences between systems A and C; system H achieves a slightly higher alveolar concentration.

RESULTS

The ages, weights, body temperatures, and end-tidal and arterialized P_{CO_2} values were similar among groups (table 1). As anticipated, an increase in inflow rate accelerated the inspired and alveolar anesthetic rate of rise for all systems (table 2, fig 2 and 3). The ratio $(F_{PO}-F_A)/(F_I-F_A)$ varied between systems, being highest in A and lowest in H (table 2, fig 4). No consistent relationship of this ratio to flow rate was found.

DISCUSSION

As anticipated, inspired and alveolar concentrations rose more rapidly at higher inflow rates. This is illustrated most dramatically during the first 10 minutes (fig 5). After 10 minutes, the curves for all systems tend to flatten, but differences between levels at different inflow rates are sustained (fig 2 and 3). The greatest effect of inflow is seen between the 1 and 3 L/min graphs: the difference between 3 and 5 L/min is relatively small. The reason for this is apparent from the figures giving the rate of rise of the inspired concentration. At 3 L/min, these already have reached 74 to 82 percent of that in the inflowing gas by 20 minutes. Thus, any further increase in inspired concentration that might be achieved by increasing the inflow rate would be limited.

The above describes the effect for halothane, a moderately soluble gas. A more

TABLE 2

Summary of Mean ± SE Values Calculated for Each System Ratio as Related to Inflow Rates

System	Flow rate	Ratio	1	2	4	6	8	10	20	30	40	50	60
A	1	F_A/F_{INFL}	0.124±0.016	0.141±0.027	0.168±0.017	0.185±0.014	0.213±0.016	0.230±0.015	0.275±0.018	0.296±0.017	0.316±0.017	0.339±0.021	0.351±0.023
	3		0.158±0.020	0.213±0.025	0.277±0.039	0.328±0.045	0.409±0.030	0.468±0.028	0.484±0.031	0.530±0.033	0.536±0.033	0.541±0.012	0.555±0.023
	5		0.253±0.048	0.304±0.052	0.433±0.027	0.487±0.055	0.516±0.069	0.518±0.054	0.558±0.039	0.599±0.041	0.634±0.035	0.660±0.039	0.694±0.034
C	1		0.127±0.012	0.131±0.017	0.186±0.021	0.215±0.023	0.241±0.021	0.273±0.018	0.310±0.025	0.336±0.030	0.368±0.028	0.360±0.027	0.369±0.021
	3		0.238±0.020	0.282±0.020	0.354±0.032	0.397±0.033	0.402±0.030	0.404±0.021	0.494±0.030	0.516±0.023	0.554±0.024	0.566±0.024	0.547±0.018
	5		0.337±0.061	0.421±0.063	0.508±0.051	0.556±0.035	0.539±0.025	0.556±0.019	0.566±0.019	0.609±0.031	0.607±0.034	0.638±0.039	0.666±0.038
H	3		0.216±0.015	0.297±0.019	0.370±0.023	0.416±0.017	0.483±0.029	0.502±0.022	0.564±0.006	0.614±0.012	0.629±0.014	0.656±0.013	0.640±0.017
A	1	F_I/F_{INFL}	0.273±0.026	0.313±0.024	0.361±0.021	0.395±0.011	0.416±0.013	0.438±0.011	0.484±0.013	0.497±0.019	0.529±0.019	0.545±0.024	0.555±0.020
	3		0.366±0.049	0.486±0.037	0.558±0.040	0.625±0.037	0.661±0.025	0.705±0.026	0.742±0.029	0.792±0.024	0.793±0.012	0.796±0.020	0.793±0.026
	5		0.542±0.088	0.528±0.069	0.725±0.050	0.758±0.036	0.775±0.024	0.806±0.035	0.802±0.032	0.838±0.023	0.852±0.032	0.849±0.026	0.856±0.044
C	1		0.229±0.018	0.294±0.019	0.355±0.022	0.396±0.027	0.415±0.032	0.440±0.035	0.501±0.033	0.535±0.018	0.551±0.010	0.551±0.015	0.564±0.013
	3		0.532±0.030	0.619±0.031	0.693±0.018	0.747±0.024	0.766±0.021	0.770±0.010	0.806±0.010	0.834±0.022	0.850±0.023	0.844±0.021	0.843±0.014
	5		0.771±0.050	0.875±0.034	0.904±0.036	0.923±0.024	0.931±0.030	0.920±0.024	0.934±0.021	0.928±0.046	0.939±0.019	0.944±0.016	0.950±0.019
H	3		0.566±0.087	0.586±0.069	0.622±0.074	0.686±0.060	0.686±0.063	0.744±0.062	0.816±0.046	0.829±0.046	0.848±0.043	0.862±0.037	0.842±0.052
A	1	$F_{PO}-F_A/F_I-F_A$	0.500±0.138	0.561±0.122	0.599±0.107	0.632±0.115	0.634±0.115	0.576±0.107	0.479±0.144	0.568±0.113	0.561±0.111	0.602±0.103	0.438±0.168
	3		0.596±0.025	0.424±0.063	0.398±0.049	0.421±0.082	0.243±0.085	0.105±0.217	0.327±0.156	0.360±0.105	0.349±0.147	0.436±0.076	0.425±0.080
	5		0.733±0.092	0.931±0.355	0.567±0.058	0.493±0.042	0.535±0.061	0.495±0.042	0.494±0.056	0.529±0.037	0.534±0.028	0.446±0.012	0.544±0.034
C	1		0.550±0.100	0.757±0.057	0.482±0.125	0.542±0.056	0.442±0.111	0.407±0.087	0.418±0.018	0.355±0.094	0.424±0.096	0.402±0.045	0.452±0.046
	3		0.519±0.105	0.524±0.068	0.432±0.059	0.356±0.106	0.474±0.048	0.430±0.055	0.362±0.116	0.446±0.043	0.416±0.043	0.387±0.057	0.400±0.062
	5		0.285±0.076	0.226±0.083	0.220±0.085	0.216±0.062	0.330±0.049	0.315±0.056	0.305±0.049	0.221±0.092	0.302±0.053	0.276±0.037	0.289±0.060
H	3		0.146±0.058	0.148±0.067	0.065±0.086	0.052±0.087	−0.049±0.049	0.003±0.058	0.016±0.045	−0.104±0.100	−0.013±0.076	−0.057±0.080	−0.011±0.052

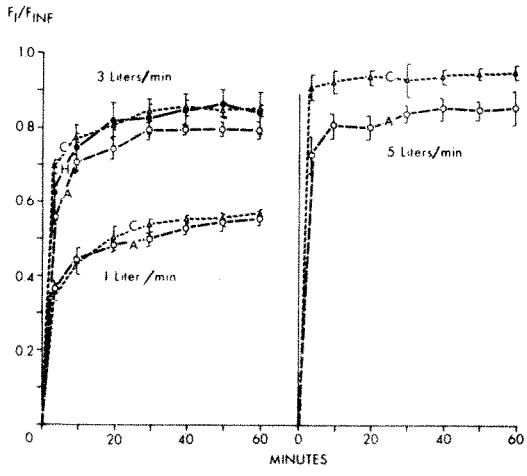


FIG 3. The inspired-to-inflow concentration ratio (F_I/F_{INF}) increases more rapidly with increasing flow rates. Both 5 L/min and 3 L/min flow rates achieve high inspired concentrations within 10 minutes. The inspired concentration at a 1 L/min inflow rate rises slowly and remains low for 1 hour. There are only slight differences between systems.

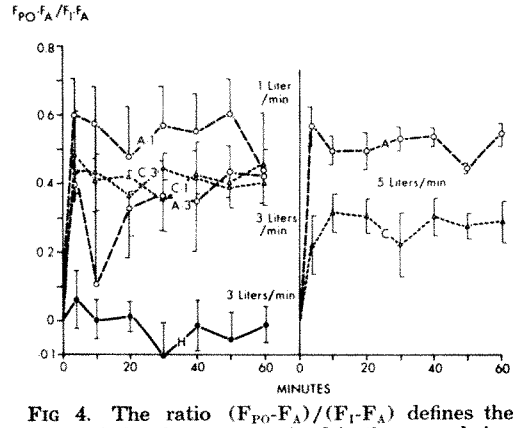


FIG 4. The ratio $(F_{PO}-F_A)/(F_I-F_A)$ defines the amount of alveolar gas contained in the gases being popped-off. A ratio of 0 would indicate only alveolar gases being evacuated and conservation of gases containing higher concentrations of anesthetic. System C is slightly more efficient that A at 1 L/min and 5 L/min, while system H is most efficient.

soluble gas such as methoxyflurane or diethyl ether might be more affected by the increase from 3 to 5 L/min, since uptake and hence rebreathing would have a greater effect on the inspired concentration.[3]

At any given flow rate, the rise of alveolar or inspired concentration to the inflow concentration tended to be slowest with system A and fastest with system H. The overflow valve position in system H permitted loss of primarily alveolar gas, thereby retaining fresh inflowing gas for rebreathing.[5] Evidence for this is seen in the low $(F_{PO}-F_A)/(F_I-F_A)$ values for system H (table 2). Although the differences between systems A and C in the above ratio are not as consistent, in general the ratio at any given inflow rate is lower with C. This accords with the prediction made in an earlier report[1] that suggested that system C conserved fresh inflow gas while system A permitted its loss through the pop-off valve.

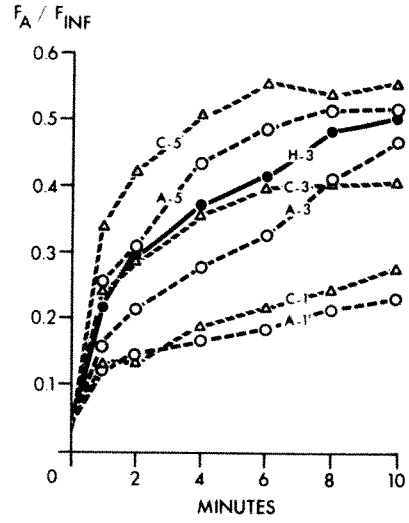


FIG 5. The rate of rise of alveolar anesthetic concentration is most rapid during the first 10 minutes of administration, and is influenced primarily by inflow rate. There is little difference between systems at any given inflow rate. Symbols along the curves refer to system and inflow rate.

Although the differences between the systems are consistent with our previous predictions,[3] they are somewhat smaller than we suggested there and are only of modest clinical significance. For halothane anesthesia, little economic gain may be realized by the choice of one system as opposed to another. A small but significant economic gain might accrue to the use of system H if the anesthetic were enflurane.* The difference between enflurane and halothane lies in the higher cost and lower potency of enflurane. Unfortunately, our data cannot be applied directly to enflurane because of the differences between enflurane and halothane solubility and uptake.

Of greater clinical and economic importance is the inflow rate. It would appear that inflow rates need not exceed 3 L/min after the first 10 minutes of anesthesia in order to sustain an inspired halothane concentration close to that delivered in the inflow.

*See Appendix.

APPENDIX

The data in table 2 for $(F_{EO}-F_A)/(F_I-F_A)$ indicate that, for system A or C, about half of the gases popped-off at a 3 L/min inflow are unabsorbed inspired gases which must be replaced. With the H system, only alveolar gas is eliminated and all inspired gas is conserved. On the average, the inspired concentration is about 50 percent higher than the alveolar concentration. If these data were applied to an alveolar enflurane concentration of 1.5 percent (a concentration giving a moderate level of anesthesia with 50 to 60 percent N_2O) they would predict a required average inspired concentration of 2.25 percent. With system A or C, half of this would be wasted but with H it would be conserved.

At a 3 L/min inflow, the wastage with A and C would equal $0.5 \times (0.0225 - 0.015) \times 3000 \times 60$, or 675 ml/hr of enflurane vapor. Since 1 ml of liquid enflurane produces 200 ml of vapor, this represents a loss of 3.38 ml liquid; each liquid ml costs approximately \$0.25, giving an hourly cost of \$0.84. Presuming 5 hours of anesthetic administration per day and 230 working days, the annual loss would be \$970, which would be regained by substituting system H for A or C. However, as noted in the discussion, our data with halothane cannot be applied directly to enflurane because of the difference in solubility.

REFERENCES

1. Eger EI II: Factors affecting the rapidity of alteration of nitrous oxide concentration in a circle system. Anesthesiology 21:348-355, 1960

2. Eger EI II: Effect of inspired anesthetic concentration on the rate of rise of alveolar concentration. Anesthesiology 24:153-157, 1963

3. Eger EI II: Effect of anesthesia circuit on alveolar rate of rise. Anesthetic Uptake and Action. Baltimore, The Williams & Wilkins Company, 1974, chapter 12

4. Eger EI II: Anesthetic systems: construction and function. Anesthetic Uptake and Action. Baltimore, The Williams & Wilkins Company, 1974, chapter 13

5. Eger EI II, Ethans CT: The effects of inflow, overflow and valve placement on economy of the circle system. Anesthesiology 29:93-100, 1968

6. Gion H, Saidman LJ: The minimum alveolar concentration of enflurane in man. Anesthesiology 35:361-364, 1971

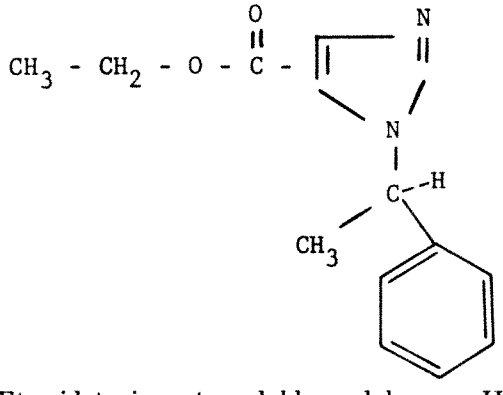
ENTERAL OXYGEN. The authors evaluated the effect of intestinal oxygen, nitrogen or carbon dioxide on the electrical activity of the stomach and intestine. The gases were injected into the intestinal lumen at a rate of 5 to 7 ml/min. Electrical activity increased with enteral oxygen but not nitrogen or carbon dioxide. Pharmacologic blockade of alpha and beta effector sites did not alter the response to enteral oxygen. The mechanism for this response is not known but unlikely explanations include increased intestinal pressure, decreased pH or reflex response. Earlier work has shown that enteral oxygen modifies the reduction in splanchnic blood flow associated with anesthesia and operation. *(Gelman S, Paz M, Levy E: Influence of enteral oxygen administration on the slow electrical activity of the intestine and stomach. Arch Surg 111: 566-574, 1976)*

Clinical Use of Etomidate for Anesthesia Induction: A Preliminary Report

ROBERT J. FRAGEN, MD*
NANCY CALDWELL, CRNA†
EDWARD A. BRUNNER, MD, PhD‡
Chicago, Illinois§

Etomidate (0.3 mg/kg) and thiopental (4 mg/kg) were administered IV for induction of general anesthesia, comparing heart rate, blood pressure, respiration, and side effects. No significant difference between the drugs was found in the circulatory parameters, but respiration was more depressed by thiopental. A high incidence of the side effects of myoclonia and pain on injection was seen with etomidate. The incidence of side effects was not affected by speed of injection or type of premedication. Mechanisms to reduce the incidence of side effects are needed for etomidate to become a useful induction agent.

ETOMIDATE, first synthesized in 1972, is (R-(+)-ethyl-1-(1-phenylethyl)-1H-imidazole-5-carboxylate sulfate. It is a new, potent, short-acting, and safe IV hypnotic with the following structural formula:



Etomidate is water-soluble and has a pH of 3.4. It is metabolized in the liver by hydrolysis of the ester group. Seventy-five percent of a single dose is excreted by the kidney in 24 hours and 13 percent is found in the feces. It is a pure hypnotic and is without analgesic activity.[1] Animal experiments and human studies have shown that etomidate causes no organ toxicity nor teratogenicity and that it has fewer side effects on the cardiovascular and respiratory systems than other short-acting IV induction agents.[1-4]

On the basis of these reports, etomidate should be expected to be a good IV induction agent for general anesthesia. It acts rapidly (one circulation time), and the duration of action of a single dose is between 4 and 10 minutes. This duration can be prolonged by increasing the dose or administering the drug as a constant infusion.[1] Etomidate would seem particularly beneficial for outpatients and patients with heart disease. However, 2 side effects have been prominent with etomidate: pain on injection

*Associate Professor.
†Research Assistant.
‡Professor and Chairman.
§Department of Anesthesia, Northwestern University Medical School, and Northwestern Memorial Hospital, Chicago, Illinois 60611.

Paper received: 1/19/76
Accepted for publication: 2/11/76

and myoclonia.* Other stimulatory effects, such as nystagmus, hypertonus, coughing, and hiccup,* have been seen with etomidate. These side effects can also be seen with barbiturates such as thiopental and methohexital.

A randomized, controlled study was undertaken to compare etomidate with thiopental with regard to blood pressure, heart rate, respiration, and side effects.

METHODS

Sixty ASA physical status I, II, and III adult surgical patients were admitted to the study (after giving informed consent). They were divided into 4 groups of 15 patients each, homogeneous for age, weight, height, and ASA status (table 1). Groups I and II received etomidate (0.3 mg/kg body weight) from a freshly prepared solution of 1.5 mg/ml lyophilized etomidate in sterile water. Group I received the injection over 30 seconds and group II over 60 seconds. Groups III and IV received 4 mg/kg of 2.5 percent sodium thiopental. Group III received the injection over 30 seconds and group IV over 60 seconds. All injections were given into the injection port of a rapidly running IV infusion of 5 percent dextrose in lactated Ringer's solution.

One-third of the patients received atropine (0.5 mg IM) 15 to 45 minutes before induction; one-third received diazepam (10 mg) and atropine (0.5 mg IM) 30 to 45 minutes before induction, and one-third received fentanyl (2 ml) and atropine (0.5 mg IM) 15 to 30 minutes before induction. Blood pressure was taken by the Riva-Rocci method, and heart rate was counted by the radial, brachial, or carotid pulse. All patients were monitored with a Tektronix® 410 cardioscope in the operating room. Blood pressure and heart rate were recorded before and 3 minutes after premdication, 3 minutes before and 1 to 2 minutes after the hypnotic, and then every 5 minutes during the course of anesthesia.

Respiratory rate was counted and the depth of respiration was observed 3 minutes before and between 1 to 2 minutes after etomidate or thiopental. The patient was observed for side effects from the onset of injection until 2 minutes after hypnotic injection. No other medications were allowed during this time except for O_2 by face mask, if necessary. Any observed changes, therefore, could be ascribed to the hypnotic. After 2 minutes, there was no restriction on the choice of anesthetic agents or technics of general anesthesia.

All patients stayed in the recovery room for the usual length of time and no restrictions were placed upon medications used there. All patients were seen 24 hours later, and, when possible, again 48 hours later, and were inspected for phlebitis at the injection site. They were also asked to rate the experience of induction of general anesthesia as good, satisfactory, or bad. An investigator (R.F.) also rated the injection. When blood pressure changes of 25 percent above or below control occurred, hypertension or hypotension were recorded as present. A similar percentage of change in heart

*Admiraal et al: Induction of anesthesia with etomidate—analysis and tabulation of 1000 case records of clinical studies (unpublished data). Janssen Pharmaceutica, Beerse, Belgium, 1974.

TABLE 1

Demographic Data

Group	I Etomidate, 0.3 mg/kg 30 sec	II Etomidate, 0.3 mg/kg 60 sec	III Thiopental, 4 mg/kg 30 sec	IV Thiopental, 4 mg/kg 60 sec
Age (average), yr	41.67	41.87	39.80	43.53
Weight (average), kg	68.93	62.13	67.93	68.47
Height (average), cm	167.27	163.80	171	169.73
Sex: Female (n)	11	12	9	8
Male (n)	4	3	6	7
ASA physical status (n)				
I	7	9	8	6
II	7	6	6	8
III	1	0	1	1

rate (25%) was considered as indicating tachycardia or bradycardia. Data were submitted to chi-square analysis.

RESULTS

There were no significant changes in blood pressure or heart rate in any group. No arrhythmias were observed during the 2-minute observation period.

Respiration rate and depth were stimulated in 6 etomidate patients, 5 in group I and 1 in group II, but were not stimulated in any thiopental patients. Either hypoventilation or apnea occurred in 15/30 patients in groups III and IV and in only 3 patients in group I. All patients in group II maintained respiration near normal.

Myoclonia, classified as mild or severe, was seen in both etomidate groups. In group I, 8 patients showed mild and 3 patients severe myoclonia. In group II, 10/15 patients had mild and none had severe myoclonia. No myoclonia was seen in groups III or IV.

Pain at the injection site occurred in 9 patients in group I, 6 patients in group II, and 1 patient in group III. In group I, pain occurred in 7/11 patients who had the IV catheter inserted in a hand or forearm vein and in 2/4 patients who had the IV in an antecubital vein. In group II, pain was experienced in 4/7 patients who had a hand or forearm IV infusion and in 2/8 with an antecubital IV infusion.

For etomidate patients, pain at the injection site occurred in 5/10 patients who received atropine only for premedication, in 6/10 who received diazepam and atropine, and in 4/10 who received fentanyl and atropine.

Hyperventilation was seen in 3/10 etomidate patients receiving atropine only and in 3/10 etomidate patients given diazepam and atropine. No patients receiving fentanyl premedication hyperventilated, and 2/3 patients who hypoventilated or were apneic after etomidate were in the fentanyl premedication group.

Nystagmus was seen in 6/30 etomidate patients ($p<0.01$), 3 each in groups I and II. Four of these patients received only atropine for premedication and 2 received diazepam and atropine. Other side effects observed are noted in table 2.

No adverse experiences occurred during maintenance of anesthesia or in the recovery room in any patient, nor was any instance of phlebitis observed.

TABLE 2

Miscellaneous Side Effects

Group / Side effect	Etomidate I 30 sec	Etomidate II 60 sec	Thiopental III 30 sec	Thiopental IV 60 sec
Coughing	1	0	0	1
Salivation	1	0	0	0
Retching	1	0	0	1
Hiccup	2	0	0	1

TABLE 3

Rating of Hypnotic by Patient and Investigation

Reaction	Good	Satisfactory	Bad
Group I Etomidate 0.3 mg/kg (30 sec)			
Patient	12	3	0
Investigator	7	2	5
Group II Etomidate 0.3 mg/kg (60 sec)			
Patient	10	4	1
Investigator	7	6	2
Group III Thiopental 4 mg/kg (30 sec)			
Patient	11	4	0
Investigator	15	0	0
Group IV Thiopental 4 mg/kg (60 sec)			
Patient	11	4	0
Investigator	14	1	0

Hypnotics were rated somewhat differently by the patients and the investigator (table 3).

DISCUSSION

All patients in the study were asleep within 1 minute of the injection of either hypnotic, and none showed any untoward effects on blood pressure or heart rate. However, we might not expect adverse cardiovascular effects in patients in ASA status I and II, nor in the 3 ASA status III patients who were under 50 years of age and were normovolemic. Since previously reported experiments[2-4] were performed on healthy

patients or dogs, etomidate should be tested in patients with known coronary artery and/or myocardial disease, to determine whether cardiac function can be maintained without increasing myocardial O_2 requirements.

Since anesthesiologists are skilled at ventilating patients and maintaining patent airways, one could question whether respiratory depression of short duration is undesirable. There was a significantly higher incidence of respiratory depression with thiopental than with etomidate ($p<0.001$). When respiration changed after etomidate, twice as many patients hyperventilated as hypoventilated; furthermore, hypoventilation occurred in 2 patients and apnea in 1. Thus, etomidate should not be used for patients in whom it may be important to maintain adequate spontaneous ventilation.

For a hypnotic drug to be useful while lacking adverse cardiovascular and respiratory side effects, it must also not have other untoward side effects. Pain on injection and myoclonia are known side effects of etomidate. In Admiraal's series of 1000 patients, myoclonia (slight, 6.7%, and severe, 4.2%) and pain on injection (11.2%) occurred. In the present study, the incidence of these side effects was higher—myoclonia, 70 percent (slight, 60%; severe, 10%) and pain on injection, 50 percent. It was thought that narcotic premedication would reduce the incidence of pain on injection and that diazepam would reduce the incidence of myoclonia, but neither happened.

The speed of injection was also thought to affect the incidence of side effects. It was noted that no severe myoclonia occurred with the 60-second injection time, but the overall incidence of myoclonia was unrelated to speed of injection. Pain on injection was less frequent with slower injection, but more patients in this group had the IV infusion placed in an antecubital vein. The diameter of the vein used for injection appears to be a more important factor than speed of injection, but the combination of slow injection and the use of a large vein appeared best. The incidence of pain on injection might also be reduced with an etomidate solution buffered to a more normal pH.

Since low-dose premedication was used in this study, it would be interesting to see what more premedication would do to the incidence of myoclonia and pain on injection. The cause of the myoclonia has not been identified, so a rational approach to reducing its incidence is not available. These side effects, although frequent, were of short duration and did not significantly affect the rating the patients gave etomidate. However, the investigator rated the induction as bad when severe myoclonia or severe pain on injection occurred.

The present study showed generally similar but slightly different results from those recently reported by Gooding and Corssen.[5]

REFERENCES

1. Rememan RS, Janssen PAJ: Experimental pharmacology of etomidate. Beerse, Belgium, Janssen Pharmaceutica, 1974

2. Bruckner JB, Gethman JW, Patsenke D, et al: Investigations into the effect of etomidate on the human circulation. Anaesthesist 23:322-330, 1974

3. Kettler D, Sonntag N, Donath N, et al: Haemodynamics, myocardial function, oxygen requirement and oxygen supply of the human heart after the administration of etomidate. Anaesthesist 23:116-121, 1974

4. Doeniche A, Gabonyi D, Lamcke H, et al: Circulatory behavior and myocardial function after the administration of three short-acting IV hypnotics—etomidate, propanidid, and methohexital. Anaesthesist 23:108-115, 1974

5. Gooding JM, Corssen G: Etomidate: an ultrashort-acting nonbarbiturate agent for anesthesia induction. Anesth Analg 55:286-289, 1976

The Anesthetic Effect of Oxygen

RAYMOND A. SMITH, DPhil*
WILLIAM D. M. PATON, DM, FRS, FRCP†

Low pressures of O_2 (3 to 5 atm) cause convulsions in mice but higher pressures produce a state very similar to anesthesia. The authors estimated the anesthetic potency of O_2 in mice which were exposed to either N_2O alone, N_2O + NaBr, or O_2 + NaBr. From the dose-response curves, ED_{50}s were derived for the gases. The ED_{50} for N_2O alone was 1.50 ± 0.036 atm (n = 12) and 1.11 ± 0.041 atm (n = 12) in the presence of NaBr, a reduction of 25 percent. The O_2 ED_{50} with NaBr was 3.91 ± 0.077 atm (n = 12). After correction for the NaBr, the ED_{50} of O_2 is estimated at 5.3 atm. This is lower than predicted from the lipid solubility of O_2.

IT IS well known that high pressures of O_2 between 3 and 5 atmospheres (atm) cause convulsions in both mice and men.[1,2] At pressures above 10 atm, the convulsant effect of O_2 in mice and rats appears to be less dominant; the convulsions are fewer and less vigorous, and the mice appear to enter a depressed state resembling that of anesthetized animals. If mice are pretreated with sodium bromide (NaBr) (800 mg/kg) the convulsant period can be eliminated, and the animals pass directly into a state of peaceful anesthesia.[3]

An interesting theoretic point arises out of this observation. Since the lipid solubility of O_2 is about 1/10 that of N_2O (Ostwald solubility coefficient in olive oil at 37° C of O_2 is 0.132, and of N_2O is 1.4) the anesthetic partial pressure of O_2, barring other effects, would be expected to be about 10 times that of N_2O (ED_{50}=1.5 atm), or 15 atm in mice. We therefore decided to estimate the potency of O_2 as an anesthetic agent and to see how well this potency correlated with its lipid solubility.

In order to test mice under high pressures of O_2, the O_2-induced convulsions must be abolished or at least heavily suppressed. Many drugs have been tested for such suppressant action. Amongst those found to have some utility are diethazine, mephenesin, trimethadione, paramethadione, chlorpromazine, and NaBr.[3] Some investigators have used sulphydryl-group-containing compounds such as glutathione, cysteine, and thiourea to provide a reducing environment which may protect vulnerable sulphydryl groups in, for example, metabolic enzymes; others have used metabolic agents, in the belief that normal cellular respiration and oxidative phosphorylation are impaired and that agents such as succinate, glutamate, glucose, or gamma-aminobutyric acid (GABA) might stimulate adenosine triphosphate production to keep up with cellular demands.[4,5]

Using these approaches, Currie's group[4] showed glutathione or cysteine combined with sodium succinate to be the most effective in postponing convulsions in dogs, although these are less effective and more variable in small rodents. Of the other drugs tested, bromide was protective at high pressures of O_2, with the least evidence of depression and, since its rate of excretion is

*Assistant Research Chemist, Department of Anesthesia, University of California Medical Center, San Francisco, California 94143.

†Professor of Pharmacology, Department of Pharmacology, Oxford University, Oxford, England.

Read at the 50th Congress of the International Anesthesia Research Society, March 14-18, 1976, at Phoenix, Arizona.

Paper received: 3/22/76
Accepted for publication: 5/3/76

very slow, a constant drug level may be expected over a long period. We decided to determine first the degree of depression caused by a bromide alone and then to use a bromide to protect mice against convulsions during the determination of the O_2 anesthetic effect.

METHODS

First we determined the partial pressure of N_2O alone required to abolish the righting reflex in half the animals tested by a rolling stimulus (the median effective dose, or ED_{50}). We used male albino mice from CD Tuck #1 stock, previously used in this laboratory for the determination of anesthetic potencies. Mice were placed individually in 300-ml stainless-steel pressure chambers equipped with close-fitting soda-lime-filled CO_2 scrubbers, which were slid up and down the chamber at regular intervals during the course of an experiment. The chambers were flushed with O_2 for 2 minutes, sealed, and then N_2O was admitted to the desired partial pressure.

The chambers were placed in a water bath maintained at 30° C, from which they were removed after an equilibration period of 15 minutes to make the test. Rotation of the chambers at 4 rpm for a total of 5 revolutions provided the stimulus. Response was scored as follows: animals which fell onto their sides and were themselves rolled through 360° twice or more during the 5-revolution sequence were assigned scores of 0. Those remaining upright or falling only once were assigned scores of 1. The resulting quantal data enabled construction of a dose-response curve from which the ED_{50} was determined, using a logit transformation by the method of Waud.[6]

Second, we determined the partial pressure of N_2O required to eliminate the righting reflex in other mice treated with the bromide. NaBr in an 8 percent aqueous solution was injected IP at a dose of 0.8 mg/gm 45 minutes before testing. Twenty-five minutes after injection, these mice were placed in the chambers, flushed with O_2 and N_2O introduced to the desired partial pressure 30 minutes after the injection. The mice were tested and results analyzed as before.

Last, the partial pressure of O_2 required to eliminate the righting reflex was determined in a 3rd group of mice. These mice were treated with the same dose of NaBr as above and after 25 minutes were placed in the chambers and flushed with O_2. O_2 was admitted to the desired pressure 30 minutes after injection and the animals were tested 15 minutes later. Responses, dose-response curves, and ED_{50} were determined.

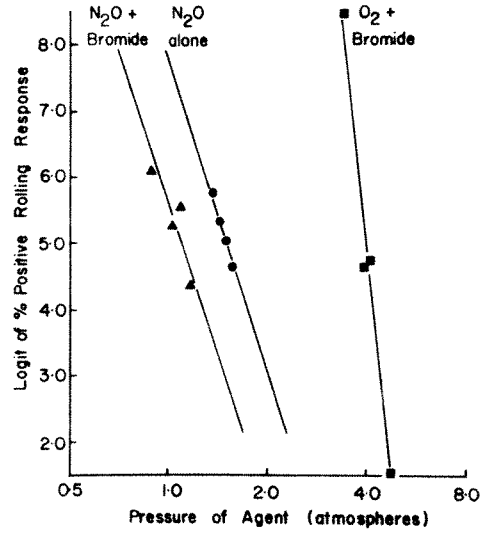


FIGURE. Dose response curves • N_2O alone. ▲ N_2O + 0.8 mg/gm NaBr. ■ O_2 + 0.8 mg/gm NaBr.

RESULTS

The 3 dose-response curves are shown in the figure, in which the logit of the percent positive response is plotted against the dose on a logarithmic scale. The reduction in the required N_2O partial pressure caused by the bromide pretreatment can be clearly seen. The ED_{50} values in gauge pressures above 1 atm of O_2 were: N_2O alone, 1.50 ± 0.036 atm (n = 12); N_2O + NaBr, 1.11 ± 0.041 atm (n = 12; and O_2 + NaBr, 3.91 ± 0.077 atm (n = 12). The dose of NaBr used reduced the N_2O ED_{50} by 26 percent of its normal value. It is also evident that the slope of the O_2 dose-response curve is somewhat steeper than that for N_2O, either with or without NaBr.

If both NaBr and N_2O and NaBr and O_2 act independently and additively, then allowing for the effect of the bromide, the O_2 ED_{50} would be 5.3 atm gauge pressure. This figure may be compared with ED_{50} values for other agents in the presence of 1 atm of O_2. Although the absolute dose of O_2 is 6.3 atm, it must be remembered that 1 atm of O_2 is almost always present in the determinations of anesthetic potency of other agents in mice.

DISCUSSION

The finding of a 25 percent contribution from NaBr to the anesthesia produced by N_2O is not surprising in view of the long history of the use of bromides as a depressant to control epileptiform convulsions. Although bromism is now rare and anesthesia during bromide intoxication unlikely, it is worth noting that the bromide can itself make a significant contribution to the total anesthetic effect.

The estimated requirement for O_2 anesthesia is less than half that expected on the basis of its lipid solubility. Two effects could contribute to alter the true requirement of O_2 for anesthesia. First the metabolic removal of O_2 from solution rather than from oxyhemoglobin would tend to lower the actual tension of dissolved O_2 in the brain leading to an overestimation of the required O_2 tension for anesthesia. Second, cerebral CO_2 tension and tissue acidity will tend to increase due to the absence of reduced hemoglobin and thus impair removal of CO_2. The degree of this latter effect is probably negligible, but would tend to underestimate the true O_2 tension for anesthesia.

A possible explanation of the greater-than-predicted potency of O_2 is that NaBr is incapable of removing completely the deleterious effects of high-pressure O_2. Since the convulsant properties of O_2 are probably mediated through the inhibition of synthesis or reduction of the levels of metabolites such as GABA,[7] it is unlikely that NaBr acts reciprocally to restore or maintain these levels. In other words, the convulsant properties of O_2 and the protective properties of NaBr are probably mediated via different mechanisms.

The NaBr may confer a certain amount of protection, by virtue of its depressant effects, against increased neuronal activity, but beyond that amount, convulsions will prevail, although in an attenuated form. In this case, the rolling response test may be unable to differentiate between the prostration following an attenuated convulsion and that associated with anesthesia. That we are indeed observing either a different mechanism of depression or even a different phenomenon with O_2 is suggested by the steeper dose-response curve compared with N_2O. The interaction of the stimulatory effects of O_2 may indicate that our assumptions concerning additivity and independence of action of NaBr and O_2 or N_2O are questionable.

REFERENCES

1. Bert P: La Pression Barometrique (1878). Translated by MA Hitchcock, FA Hitchcock, Columbus, Ohio, Longs College Book Company, 1943

2. Donald KW: Oxygen poisoning in man. Br Med J 1:667-712, 1947

3. Paton WDM: Experiments on the convulsant and anaesthetic effects of oxygen. Br J Anaesth 29: 350-366, 1967

4. Currie WD, Gelein RM Jr, Sanders AP: Effects of hyperbaric oxygenation on metabolism. VI. Efficacy of protective agents at 5, 7, 9 and 11 atmospheres of 100% O_2. Proc Soc Exp Biol Med 133:103-105, 1970

5. Currie WD, Gelein RM Jr, Sanders AP: Comparison of protective agents against hyperbaric oxygen in large animals. Aerosp Med 44:996-998, 1973

6. Waud DR: On biological assays involving quantal responses. J Pharmacol Exp Ther 183: 577-607, 1972

7. Wood JD, Watson WJ: Gamma-aminobutyric acid levels in the brain of rats exposed to oxygen at high pressures. Can J Biochem 41:1907-1913, 1963

Case History Number 92: Prolonged Apnea After Succinylcholine in a Dental Outpatient

RICHARD G. McLAREN, MB*
EMERSON A. MOFFITT, MD†
Halifax, Canada‡

A 28-YEAR-OLD man, 185 cm tall and weighing 77.3 kg, was admitted as an outpatient for dental extractions under general anesthesia. There were no positive findings in his history; he had had an uneventful tonsillectomy as a child, details on the anesthetic are not known but it seems highly unlikely that he received succinylcholine (SCh). On admission, all physical and laboratory findings, including hemoglobin and urinalysis, were within normal limits.

He came to the operating room unpremedicated, and after atropine (0.6 mg) IV, anesthesia was induced with sodium thiopental (350 mg). Succinylcholine (80 mg) was given to facilitate nasotracheal intubation. Anesthesia was maintained with halothane-N_2O-O_2. Initially, he was ventilated manually, but apnea persisted following the SCh despite CO_2 challenge, obtained by hypoventilation and increasing the inspired concentration. Accordingly, mechanical ventilation was instituted. At no time were there untoward changes in his pulse and blood pressure; the operation proceeded uneventfully.

At the end of operation, he was transferred to the recovery room with the endotracheal tube in place, under controlled manual ventilation. Spontaneous respiratory activity returned after arrival in the recovery room, approximately 60 minutes after the SCh injection. The patient's minute volume increased to 5 L/min and he began coughing on the endotracheal tube. Peripheral muscle tone was still clinically reduced, but he was conscious and alert and was therefore extubated. A blood sample was taken for pseudocholinesterase activity and phenotyping. He was discharged home 2 hours postoperatively with no residual effects.

The cholinesterase estimation, by the King modification of the Kalow-Lindsay method,* showed pseudocholinesterase, 588 mμ/ml (normal 620 to 1370 mμ/ml), dibucaine 18, fluoride 21, chloride 55. These results indicate that the patient is an atypical homozygote for cholinesterase, an E_1^a E_1^a phenotype. He is thus invariably at risk regarding SCh apnea and has been so advised. Unfortunately, surviving members of the patient's family are not available for phenotyping.

*See references following discussion.

*Resident.
†Professor and Head.
‡Department of Anaesthesia, Faculty of Medicine, Dalhousie University, Halifax, Canada.

Comment

EMERSON A. MOFFITT, MD

Soon after SCh began to be used clinically, it was found that prolonged apnea, after a small dose, occurred in a small proportion of patients. The causal relation to low serum levels of cholinesterase was brought out between 1955 and 1960 by Dr. Walter Kalow of the University of Toronto. Since then, more work on this subject has been done by many investigators, among them Dr. King at the Royal Infirmary, Glasgow.

Succinylcholine apnea can be easily managed by artificial ventilation. But it still occurs unexpectedly, as seen here in a dental outpatient. When it does, phenotyping of the patient and family should be done, that they may alert the anesthesiologist prior to future anesthetic procedures.

Guest Discussion

J. KING, BSc, PhD
Department of Biochemistry
Royal Infirmary
Glasgow, Scotland

M. J. McQUEEN, MB, ChB, PhD
Department of Biochemistry
Camp Hill Hospital;
Pathology Department
Dalhousie University
Halifax, Canada

The pharmacologic properties of succinylcholine were first described in 1906,[1] but its value as a short-acting muscle relaxant was not realized until 1949.[2] Since then, many cases similar to this have been described. It provides a timely reminder that since it is well understood in modern anesthetic practice, this phenomenon does not represent a major hazard to the patient. It is, however, a legitimate cause for concern, and may demand prolonged intensive attention.

This patient did not exhibit spontaneous respiratory activity until approximately 60 minutes after the SCh injection. The apneic response is due to an alteration in the enzyme molecule which results in the drug not being hydrolyzed as rapidly as normally and thereby prolonging the effect. This molecular change carries only a pharmacologic, not a physiologic, penalty.

Before discussing the relationship between enzyme levels and the length of the apneic episode, we would like to stress the need for adherence to international agreements relating to enzyme nomenclature. In human tissues there are 2 enzymes which hydrolyze choline esters.[3] Several terms have been used for the enzyme which predominates in nerve tissue and is also present in erythrocytes, including "specific," "true," "aceto," or "e-type" cholinesterase. The liver-synthesized enzyme found in blood serum has been called "nonspecific," "pseudo," "butyro," or "s-type" cholinesterase.

Such a proliferation of names has served to confuse. The modern nomenclature, while recognizing that these hydrolases have overlapping substrate specificities, acknowledges that the nerve and erythrocyte enzyme directs its specificity toward acetyl esters and is called acetylcholinesterase (E.C.3.1.1.7, acetyl choline acetyl-hydrolase). The serum enzyme of interest in this case report directs its specificity toward choline esters and is correctly called cholinesterase (E.C.3.1.1.8, acylcholine acyl-hydrolase).

Apart from the confusing biochemical terminology, the multiplicity of methods and reference values with which anesthesiologists have been bombarded, a major problem has been in attempting to correlate the sensitivity of the patient with the reported cholinesterase activity and inhibitor numbers. The present "state of the art" indicates that 50 percent of cases of SCh apnea cannot be predicted[4,5] and occur in individuals who are homozygotes or heterozygotes for the usual enzyme ($E_1^uE_1^u$; $E_1^uE_1^s$; $E_1^uE_1^a$; $E_1^uE_1^f$). A screening procedure to cover all patients being served by the surgical services in a 3,000,000 population area would reveal 1 patient every 10 days with a predictably sensitive phenotype. Unfortunately, during the same period 1 unpredictable SCh apnea would have occurred.[6] This is not the basis for a satisfactory screening program, particularly when modern anesthetic practice can handle the apneic problem so well. There is no significant morbidity or mortality directly attributable to SCh apnea which

requires to be balanced against a limited success rate for screening.

A linear relationship does not exist between reported cholinesterase activity and sensitivity in individuals of predictable sensitivity. As a generalization, it is true that the lower the cholinesterase activity and dibucaine and fluoride numbers, the more prolonged the apneic response to succinylcholine. It is necessary to consider the biochemical procedures in use in order to understand why this relationship is not invariably present.

The assay procedure for cholinesterase activity reported in this case was that of Kalow and Lindsay[7] modified by King[8] and measured at 25° C. There is a wide overlap of activities from all phenotypes, and a number of SCh-sensitive people have normal cholinesterase activities. When the same procedure is carried out at 37° C, the distribution of activities for the usual homozygotes shows no significant changes. However, the activities of the SCh-sensitive phenotypes is substantially reduced and none remain in the normal range. This indicates that a valid assay of cholinesterase activity can be carried out only at 37° C. Such an assay shows a good correlation between cholinesterase activity and patient sensitivity.

However, it has been shown[9] that accurate phenotyping requires at least two inhibitor numbers, of which one must be fluoride. The phenotype discrimination of dibucaine can be retained at 37° C, but no manipulation of substrate and inhibitor concentrations preserves the discriminatory ability of fluoride at 37° C. On balance, we believe that it is better to be able to phenotype precisely and, hopefully, avoid future problems for the patient and his family, rather than to have the enzyme activity correlate with the patient sensitivity after the event has occurred.

Little attention appears to have been paid to the effects of substrate and temperature on the predictive value of the test. It has already been pointed out[10] that in an official selected method of the American Association of Clinical Chemists,[11] the combination of the substrate propionylthiocholine and a reaction temperature of 37° C results in poor phenotype discrimination. A recent report[12] has supported aspects of this earlier observation.

It is also indicated in the present case report that phenotyping of the patient's family is desirable. While we do not consider population screening to be a worthwhile exercise, we do agree strongly that phenotyping should be offered to close blood relatives of any patient who has had an SCh apnea. Sensitivity cards can then be issued to all individuals of the 4 phenotypes invariably at risk: $E_1^aE_1^a$, $E_1^aE_1^f$, $E_1^fE_1^f$, and $E_1^sE_1^s$.

Not enough attention generally seems to be paid to the necessity of assuring the patient and his family that current knowledge knows of no other genetic problems or drug sensitivities associated with these phenotypes. Patients are also reassured by the knowledge that the existence of other muscle relaxants means that any future operations they may require will not be a major departure from normal anesthetic procedure.

REFERENCES

1. Hunt R, Taveaux R deM: On the physiological action of certain cholin derivatives and new methods of detecting cholin. Br Med J 2:1788-1791, 1906

2. Bovet D, Bovett-Nitti F, Guarino S, et al: Proprieta farmacodinamiche di alcuni derivati della succinilocolona datati di azione curavica. RC Inst Sup Saint 12:106-110, 1949

3. Alles GA, Hawes RG: Cholinesterases in the blood of man. J Biol Chem 133:375-390, 1940

4. Telfer ABM, McDonald DJF, Dinwoodie AJ: Familial sensitivity to suxamethonium due to atypical pseudocholinesterase. Br Med J 1:153-156, 1964

5. Lehmann H, Liddell J: Human cholinesterase (pseudocholinesterase) genetic variants and their recognition. Br J Anaesth 41:235-244, 1969

6. King J: Studies on human serum cholinesterases. University of Glasgow, PhD Thesis, 1974, pp 128-130

7. Kalow W, Lindsay HA: A comparison of optical and manometric methods for the assay of human serum cholinesterase. Can J Biochem 33: 568-574, 1955

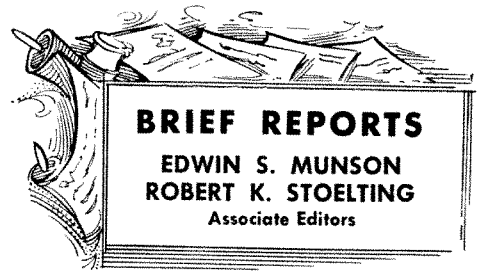
8. King J: Practical Clinical Enzymology. London, Van Nostrand, 1965

9. King J, Griffin D: Relationship between suxamethonium apnoea, serum cholinesterase activity and inhibitor numbers. Br J Anaesth 46:908-911, 1974

10. King J: Studies on human serum cholinesterase. University of Glasgow, PhD Thesis, 1974, pp 114-115

11. Dietz AA, Rubinstein HM, Lubrano T: Colorimetric determination of serum cholinesterase and its genetic variants by the propionylthiocholine dithiobis (nitrobenzoic acid) procedure. Clin Chem 19:1309-1313, 1973

12. Price EM, Brown JJ: Scope and limitations of propionylthiocholinesterase in the characterization of cholinesterase variants. Clin Biochem 8: 384-390, 1975



A Precordial ECG Lead for Chest Operations

BRIAN DALTON, MD*

THE limitations of the standard ECG limb leads in detecting myocardial ischemia have led to the adoption of various left precordial leads (V_4, V_5, CS_5, or CM_2) in stress testing of coronary heart disease patients.[1] During anesthesia in such patients, tachycardia, hypertension, excessive myocardial contractility, hypotension, and hypoxia may invoke myocardial distress. Use of a precordial lead to detect myocardial ischemia does not appear to be widely practiced. Objections include prior skin trauma and, in thoracic operations, concern about proximity to the sterile area.

A sterile technic has been used in over 1500 cardiac operations performed through a median sternotomy. After completion of the preoperative bacteriocidal preparation of the skin, a sterile all-metal spinal needle is inserted in the V_4 or V_5 area. One end of a sterile 15-meter-long insulated wire with alligator clips at either end is attached to the needle hub (fig 1). The needle and adjacent wire are secured to the chest with sterile adhesive sheet plastic and sterile draping is completed. The free end of the insulated wire is connected to the precordial exploring lead of a conventionally applied ECG cable.

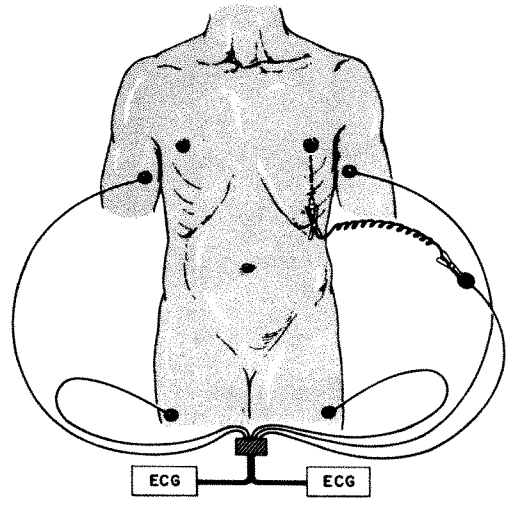


FIG 1. Schema of sterile needle and wire connected to the precordial (exporing) electrode and 2 electrocardiographs.

*Assistant Professor, from the laboratories of the Department of Anesthesia, Harvard Medical School at the Massachusetts General Hospital, Boston, Massachusetts 02114.

This study was supported in part by US Public Health Service Grant #GM15904-08.

Paper received: 12/17/75

Accepted for publication: 2/3/76

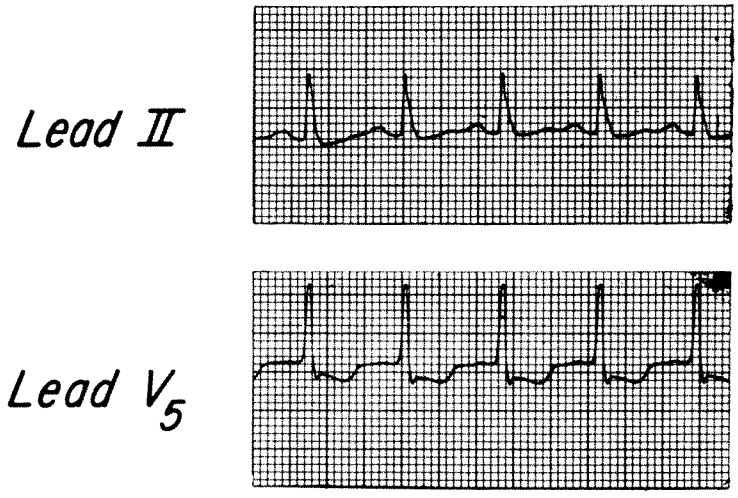


FIG 2. Simultaneous ECG tracings displaying ST segment depression in V_5 only.

A second ECG allows simultaneous recording of a precordial and standard lead. ST segment depression characteristic of subendocardial ischemia is frequently observed in only the precordial lead (fig 2).

No complications involving pneumothorax, hemorrhage, or electric burns have been encountered. To prevent burns at the site of ECG electrode placement during use of an electrosurgical unit, inductors have been recommended[2,3] to provide essential energy return.

REFERENCES

1. Redwood DR, Epstein SE: Uses and limitations of stress testing in the evaluation of ischemic heart disease. Circulation 46:1115-1131, 1972

2. Becker CM, Malhotra IV, Hedley-Whyte J: The distribution of radio frequency current and burns. Anesthesiology 38:106-122, 1973

3. Finlay B, Couchie E, Boyce L, et al: Electrosurgery burns resulting from use of miniature ECG electrodes. Anesthesiology 41:263-269, 1974

A Safety Valve for the Pediatric Rees System

SIVAM RAMANATHAN, MD*
JACK CHALON, MD†
HERMAN TURNDORF, MD‡
New York, New York§

TAYLOR and Stoelting[1] have pointed out the dangers associated with the use of the Rees pediatric system: (1) pneumothorax, which may follow a sudden rise in system pressure caused by inadvertent kinking of the free-flow connector, malfunction of the bag-tail pop-off valve, or accidental use of the O_2 flush mechanism with the bag-tail pop-off closed, and (2) complications (or death) arising from spillage of liquid anesthetics from the vaporizer into the T-piece, caused by the sudden release of a kink in

*Assistant Professor of Anesthesiology.
†Associate Professor of Anesthesiology.
‡Professor and Chairman, Department of Anesthesiology.
§Department of Anesthesiology, New York University Medical Center, New York, New York 10016.
Reprint requests to Dr. Chalon.
Paper received: 12/29/75
Accepted for publication: 2/10/76

the delivery tube in a system constructed without a liquid trap. Rees[2] also has mentioned the high system pressure that may result from the manual compression of small bags in which the force per unit area ratio is high. Although pressure-release systems have been advocated at the patient end of the system,[1] we have investigated the use of a safety valve placed at the common gas outlet of the anesthesia machine.

METHODS

The pressure-release mechanism of a Hope pediatric resuscitator,* the most commonly used pediatric resuscitator bag,[3] was employed to devise a safety valve for the Rees system. The patient end of the Hope resuscitator was removed from its inflator bag. This plastic assembly consists of a nonrebreathing valve, a pressure-relief valve set to pop off at 31 torr, and a tube-mask mount. The nonrebreathing valve was removed by unscrewing it from its plastic seat. The orifice through which the valve had been removed was then sealed. The modified plastic assembly, now only incorporating the pressure-relief mechanism, was then attached to the common gas outlet of an anesthesia machine by its bag attachment port, and placed in such a fashion that the tube-mask mount faced upward (fig 1).

The machine end of the gas delivery tube of a Rees pediatric system was joined to the tube-mask mount of the resuscitator by a 6-mm endotracheal-tube connector. The Rees system was composed of a 0.5 L anesthesia bag with a tail pop-off valve, a 30-cm corrugated free-flow connector, a T-piece, and an elbow connector with a side arm. Finally, a 1 L anesthesia bag was attached to the patient end of the elbow connector, and the side arm of the elbow connector was joined to a pressure transducer by a short piece of tubing. The transducer was electrically connected to a multichannel recorder. The anesthesia system was used with a 5 L/min fresh gas flow and the bag tail was closed.

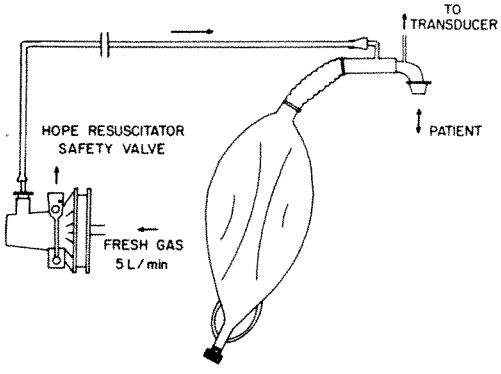


FIG 1. Jackson-Rees system attached to pressure-release system of an Ohio Pediatric Hope Resuscitator. The patient end is connected to a 1-L anesthesia bag for the experiments shown in figure 2.

*Ohio Medical Products, Madison, Wisconsin.

Three sets of pressure recordings were made: (1) without applying pressure on the bag of the Rees system, (2) by strongly compressing the bag, and (3) with the O_2 flush valve of the anesthesia machine at first partly and then fully opened.

RESULTS

In the pressure tracings shown in figure 2, panel A depicts the pressure recording when a 5 L/min fresh gas inflow only is introduced into the system. Over a 4-second period, the pressure gradually rises from 15 to 30 torr and then drops back abruptly to 15 torr within 1 second, after which the

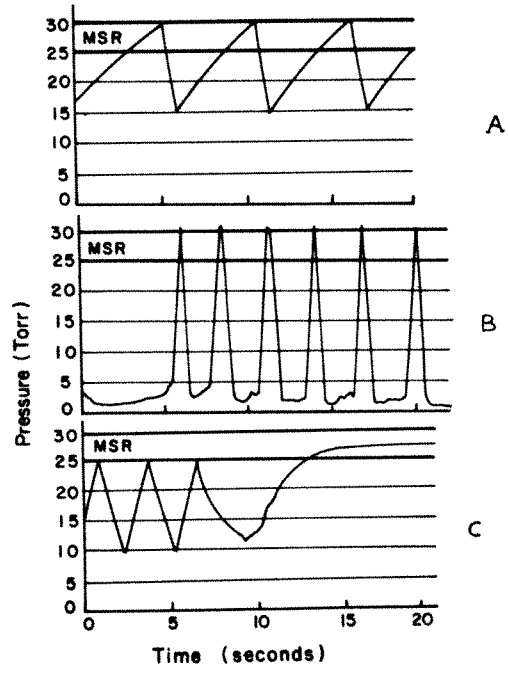


FIG 2. Pressure variations within the Rees system with a fresh gas flow of 5 L/min and without gas escape from the bag tail: Panel A: With constant flow and without external compression of the bag. Panel B: With forcible manual compression of the bag. Panel C: Without external compression of the bag but with the O_2 flush system at first partially and later fully operating. MSR = maximum safe pressure range.

cycle is repeated. Panel B demonstrates the pressure variations within the system when the bag is forcibly compressed manually. Maximum pressures recorded do not exceed 31 torr. Panel C is a tracing of system pressures when the O_2 flush of the anesthesia machine is at first partly and later fully opened; the curve obtained is at first similar to that depicted in panel A but the pressures reached are lower (10 to 25 torr). Later, when the O_2 flush valve is fully opened, system pressure rises to and remains at 27 torr.

DISCUSSION

All experiments showed that, under the conditions studied, the pressure within the Rees system never rose above 40 cm H_2O (31 torr), which is below the safe maximum limit of 50 cm H_2O advised by Avery.[4] In addition, the pressure-release valve assembly can also act as a receptacle for accidentally spilled liquid anesthetics so long as the tube-mask adapter is placed face upward. Fitting this device at the machine end of the system eliminates the addition of bulky components within the anesthesia circuit, as recommended by Taylor and Stoelting.[1]

We strongly recommend the use of this instrument whenever a Rees system is used, as it will prevent the development of pneumothorax caused by a sudden rise in system pressure or the inhalation of liquid anesthetics. The eventual manufacture of this apparatus will avoid the dismantling of existing equipment.

REFERENCES

1. Taylor C, Stoelting VK: A modified Ayre's T-tube technic—anesthesia for cleft lip and palate surgery. Anesth Analg 42:55-62, 1963

2. Rees, GJ: Anaesthesia in the newborn. Br Med J 2:1419-1422, 1950

3. Lough MD, Doershuk CF, Stern PC: Pediatric Respiratory Therapy. Chicago, Year Book Medical Publishers, Inc, 1964, p 121

4. Avery ME: The Lung and Its Disorders in the Newborn Infant. Second edition. Philadelphia, WB Saunders Company, 1968, p 242

Hazards of Disposable Rebreathing Circuits

JAMES E. COTTRELL, MD*
WILLIAM BERNHARD, MD†
HERMAN TURNDORF, MD‡
New York, New York§

THE use of disposable rebreathing circuits has increased greatly in the past decade, largely because of the decreased likelihood of pulmonary cross-contamination.[1,2] We have noticed that circuits frequently are defective as delivered by the manufacturer. The most frequently seen faults include:

1. Kinking, which occurs easily in some circuits (fig 1-a). Partial kinking will markedly increase the resistance to breathing. Complete kinking, if not detected, may be life threatening.

2. Indentation into the breathing circuit lumen (fig 1-b), which may disturb laminar air flow enough to increase system flow resistance.[3]

3. Fractures in the polyethylene connectors (fig 2-a) that create leaks large enough to decrease gas delivery to the patient. This is particularly hazardous during mechanical

*Assistant Professor of Anesthesiology.

†Associate Professor of Anesthesiology.

‡Professor and Chairman, Department of Anesthesiology.

§New York University Medical Center, New York, New York 10016.

Paper received: 12/12/75
Accepted for publication: 3/2/76

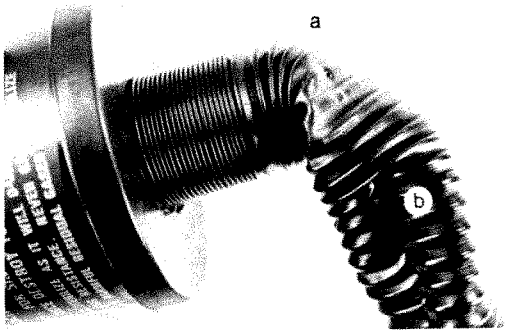


FIG 1. a. Kinking of a circuit. b. Indentation into the breathing-circuit lumen.

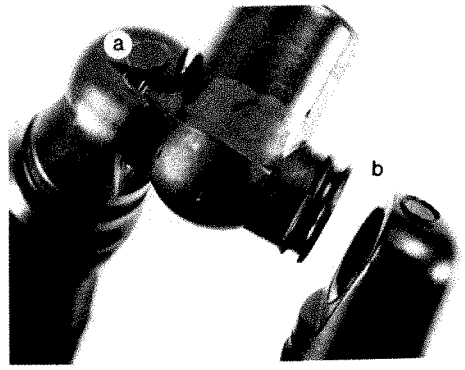


FIG 2. a. Fracture in the polyethylene connectors. b. Separation at the swivel connector.

ventilation or closed-circuit anesthetic administration, and theoretically may create hazards to operating-room personnel because of environmental pollution.[4,5]

4. Separation of the swivel connector of some circuits (fig 2-b), which occurs commonly and may be difficult or even impossible to restore during an anesthetic procedure.

5. Leaks, which have been noted at connector sites, as well as at various sites along the corrugated tubing itself. Because such leaks are not ordinarily anticipated, they may not be looked for when they occur. Scavenger devices, of course, are ineffective at these sites.[6]

One of the disadvantages of disposable circuitry has been increased cost. If circuits must be discarded because of defects, real costs become higher.

Disposable anesthesia circuitry may be a potential source of unexplained airway obstruction or leak; close inspection of anesthesia circuitry before use is therefore mandatory. Sufficiently rigid quality control must be initiated to avoid unnecessary hazards to patients as well as to attending personnel.

REFERENCES

1. Parmley JB, Tahir AH, Dascomb HE, et al: Disposable versus reusable rebreathing circuits: advantages, disadvantages, hazards and bacteriologic studies. Anesth Analg 51:888-894, 1972

2. Joseph JM: Disease transmission by inefficiently sanitized anesthetizing apparatus. JAMA 149:1196-1198, 1952

3. Dorsch JA, Dorsch SE: Understanding Anesthesia Equipment. Baltimore, The Williams and Wilkins Company, 1975, p 141

4. Cohen EN, Brown BW, Bruce DL, et al: Occupational disease among operating room personnel: a national study. Anesthesiology 41:321-340, 1974

5. Corbett TH: Inhalation anesthesia: an occupational hazard. Hosp Practice 9:81-88, 1974

6. Corbett TH: The gas trap: a device to minimize chronic exposure to anesthetic gases. Anesthesiology 31:464, 1969

A PEEP Device for a Manual Bag Ventilator

AZRIEL PEREL, MD*
DAN EIMERL, MD†
MORRIS GROSSBERG, IRIT‡
Jerusalem, Israel§

PEEP (positive end-expiratory pressure) is one of the major therapeutic technics in the treatment of various forms of adult respiratory-distress syndrome. Commonly used volume respirators have built-in PEEP valves. There are, however, situations in which the patient cannot be ventilated by a mechanical respirator, such as during transportation within or to another hospital. Ventilation is then usually accomplished using a manual bag ventilator. The discontinuation of PEEP can be hazardous in patients with severely compromised oxygenating capacity, since Pao_2 may decrease immediately when ventilation in these patients is changed from continuous to intermittent positive-pressure.[1]

The usual means of maintaining PEEP while the patient is disconnected from the respirator is by submerging an extension from the expiratory valve below water or by using a weight-operated valve. These methods require that the PEEP device be maintained in the upright position. We propose, instead, the use of the Exhalation Pressure Valve* originally designed to produce continuous positive airway pressure during spontaneous ventilation.

The exhalation pressure valve consists of a body with a spring-loaded exhalation valve. A knob adjusts the exhalation pressure between 0 and 6 cm H_2O. Calibration marks indicate the pressure setting.

The valve is attached to the expiratory port of a manual respirator with a short length of corrugated rubber tubing (figure). The end-expiratory pressure can be controlled by adjusting the pressure knob. This simple device enables the maintenance of PEEP within the limits of the apparatus (up to 6 cm H_2O) without the difficulties involved in maintaining the PEEP device upright during transport. It also provides better oxygenation while inflating the lungs during physiotherapy and suction procedures in patients with respiratory failure. It may further prove useful in the early institution of PEEP in battle casualties with pulmonary edema, after initial resuscitation.

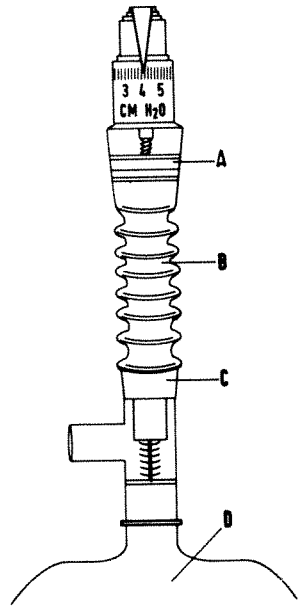


FIGURE. Exhalation pressure valve (A) connected with a short corrugated tube (B) to the expiratory port (C) of a manual respirator (D). The tube is attached to the side adapter between C and D.

REFERENCE

1. Kumar A, Falke KJ, Geffin B, et al: Continuous positive pressure ventilation in acute respiratory failure. N Engl J Med 283:1430-1436, 1970

*Ohio Medical Products, Madison, Wisconsin.

*Instructor in Anesthesiology.
†Instructor in Anesthesiology.
‡Head of Respiratory Therapy.
§Respiratory Intensive Care Unit, Department of Anesthesiology, Hadassah University Hospital, Jerusalem, Israel.

Paper received: 1/15/76
Accepted for publication: 3/25/76

The Tracheal Bronchus: An Unusual Airway Problem

TAMERISA VENKATESWARLU, MD*
CECIL J. TURNER, MD†
JAMES D. CARTER, MD‡
DEAN H. MORROW, MD§
Houston, Texas‖

ANATOMIC abnormalities of the airway are of particular concern to the anesthesiologist. This report, which describes a patient with a congenital tracheal bronchus, is presented to alert the anesthesiologist to an unusual developmental defect of potential importance in airway management.

REPORT OF A CASE

A 2-year-old girl was admitted to the hospital with a history of recurrent croup. The child had experienced recurrent pulmonary infections, bronchiolitis, and asthma since 2 months of age. At the time of admission, the mother described fairly characteristic croup symptoms which seemed to coincide with periods of moderate exercise. The past medical history was negative except for several hospitalizations related to the present illness. Approximately 1 year before the present admittance, cardiac catheterization had ruled out a left pulmonary arterial vascular ring.

Physical examination on admission showed inspiratory and expiratory stridor. Hemoglobin, hematocrit, and WBC were within normal limits. Immunoglobulins were normal and a sweat test was negative. Throat culture grew a mixed bacterial flora. The admission chest x-ray was considered consistent with nonspecific peribronchial disease. Two series of esophagograms, a week apart, were inconclusive for the presence of a vascular ring.

The child was placed in a croup tent and treated with IPPB using racemic epinephrine, and with parenteral ampicillin. On the 10th hospital day, bronchoscopy was performed under halothane anesthesia. The postbronchoscopy diagnosis was deformity of the carina, of unknown etiology. Two days later, bronchograms were obtained under general endotracheal anesthesia using the same agents. This study revealed a right tracheal bronchus arising approximately 2.5 cm proximal to the carina (figure). Two days later the child was discharged with arrangements for home respiratory therapy.

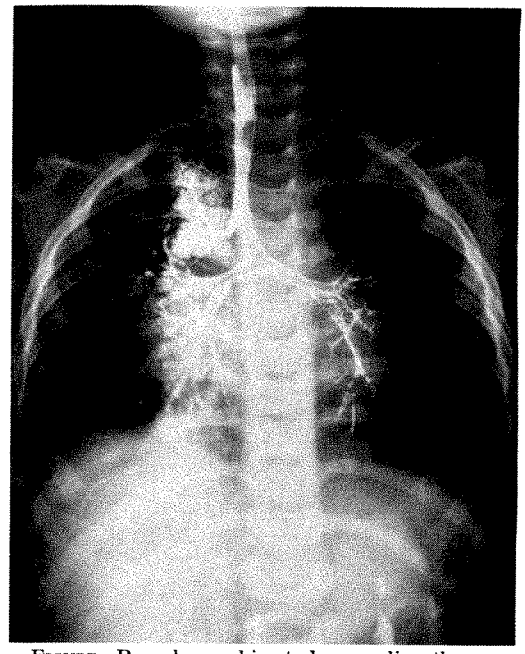


FIGURE. Bronchographic study revealing the presence of an apical displaced, right tracheal bronchus. The left tracheal shadow at the level of the 1st rib is suggestive of a vascular ring, although this was not verified by cardiac catheterization or esophagograms. The potential for inadvertent intubation or occlusion of this lower airway anomaly is apparent.

*Resident in Anesthesiology.
†Clinical Instructor of Anesthesiology.
‡Clinical Instructor of Anesthesoilogy.
§Professor of Anesthesiology.
‖Department of Anesthesiology, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas 77030.

Paper received: 1/29/76
Accepted for publication: 3/8/76

COMMENT

The respiratory tract originates from the anterior division of the embryonic foregut at about 4 weeks of gestation.[1] The tracheobronchial diverticulum originates in the pharynx and divides into the 2 major bronchial branches which subsequently give rise to the segmental bronchi, bronchioli, terminal bronchi, and alveoli.[2] During the 1st weeks of life, a tracheal bronchus is present but usually resorbs in the human, although it persists as a normal anatomic feature in swine, cattle, sheep, and other ruminants.[3]

Two variants of the persistent tracheal bronchus have been reported: (1) the supernumerary, which is an additional airway supplying the right upper lobe, and (2) the more-common apical displaced variant, in which the bronchus to the right apical lung segment arises directly from the trachea.[1] As can be seen in the figure, the apical displaced variant was present in the child described.

To our knowledge, this is the 2nd report of a tracheal bronchus in infancy and childhood. The first, reported by Iancu and colleagues,[1] was in a 7-month-old boy. However, comments by bronchoscopists suggest that this form of airway anomaly may be more frequent than the literature indicates.

From a practical clinical point of view, inadvertent intubation or occlusion of the tracheal bronchus with secondary unanticipated ventilatory difficulties are significant potential hazards in patients with this congenital anomaly. Bronchial intubation during the 2nd anesthetic procedure in our patient could have resulted had the endotracheal tube been advanced an additional 3 to 4 cm, resulting in overdistention of the right upper lobe, with compression of adjacent lung tissue or pneumothorax. Additionally, this airway segment could easily be occluded by the cuff of an endotracheal tube, causing collapse of the lobe.

Thus, although statistically uncommon, the presence of a persistent tracheal bronchus warrants consideration in the differential diagnosis of unanticipated airway problems, particularly those which occur following intubation.

REFERENCES

1. Iancu T, Boyanover Y, Eilam N, et al: Infantile sublobar emphysema and tracheal bronchus. Acta Paediatr Scand 64:551-554, 1975

2. Harrison RG: A Textbook of Human Embryology. Oxford, Blackwell Scientific Publications, 1959, p 103

3. Warkany J: Congenital Malformations, Notes and Comments. Chicago, Year Book Medical Publishers, Inc, 1971, p 600

SUBCUTANEOUS HEPARIN. The effect of low dose heparin prophylaxis on the incidence of vein thrombosis, surgical bleeding and wound hematoma, was determined after abdominothoracic surgery. Subcutaneous heparin, 5000 units, was administered two hours preoperatively and then every eight hours postoperatively for seven days. The incidence of vein thrombosis was reduced from 16 percent in control patients to 3.6 percent with heparin prophylaxis. More significantly, the incidence of popliteal or femoral vein thrombosis was reduced from 2.9 percent to 0.8 percent. Heparin prophylaxis resulted in clinically insignificant increases in blood loss, wound hematoma and fall in hematocrit. *(Gallus AS, Hirsh J, O'Brien SE et al: Prevention of venous thrombosis with small subcutaneous doses of heparin. JAMA 235:1980-1982, 1976)*

Innominate Artery Compression Simulating Cardiac Arrest During Mediastinoscopy: A Case Report

JAE-HWAN LEE, MD*
ANTHONY SALVATORE, MD†
White Plains, New York‡

MEDIASTINOSCOPY has become a recognized means of diagnosis and of determination of resectability, bronchogenic carcinoma, sarcoidosis, and other mediastinal masses. A case is presented of innominate (brachiocephalic) artery compression simulating cardiac arrest, with severe bradycardia, during mediastinoscopy. Unusual problems and anatomic relationships are described, and the importance of continuous monitoring during mediastinoscopy is stressed.

Carlens[1] first described mediastinoscopy, the technic of examining the paratracheal, subcarinal, and suprahilar areas of the mediastinum, in 1959. Since that time, the procedure has become generally familiar for diagnosis and preoperative evaluation.[2-5]

The rationale for mediastinoscopy depends on the fact that intrathoracic lymphatic drainage is from the periphery of the lung toward the centrally placed paratracheal lymph nodes. Previous mediastinoscopy is an absolute contraindication, because scarring eliminates the plane of dissection. Severe tracheal deviation, vascular problems such as thoracic aneurysms, and increased pressure in the superior vena cava are relative contraindications.[2]

An alarming and potentially dangerous intraprocedural event may be the appearance of innominate artery compression, as described following.

REPORT OF A CASE

A 27-year-old black girl was hospitalized with a persistent cough associated with dyspnea of 1-month duration. Her medical history was otherwise unremarkable. Chest x-rays showed marked hilar adenopathy with an interstitial fibrotic pattern throughout the lung fields. Other laboratory findings were normal. She underwent mediastinoscopy on the 5th day of hospitalization. Preanesthetic medication consisted of 10 mg of morphine sulfate and 0.4 mg of scopolamine. Anesthesia was induced with 250 mg of thiopental, intubation of the trachea was facilitated with 40 mg of succinylcholine, and anesthesia was maintained with enflurane-N_2O-O_2. Ventilation was assisted manually.

The patient was placed supine with a pillow under the shoulders to extend the head slightly, with the head up about 15° to relieve venous congestion. We monitored the arterial pressure of the right arm by cuff, digital pulse with a Datascope® finger plethysmograph, and heart action by ECG lead II. Fifteen minutes after the mediastinoscopy was started, the finger plethysmographic tracing suddenly disappeared. There was no recordable blood pressure and no right radial pulse in the presence of a normal ECG tracing. Cardiac arrest was suspected and the mediastinoscope was quickly removed.

Immediately after withdrawal of the mediastinoscope, a normal plethysmographic tracing was restored, with adequate blood pressure and radial pulsation. No further treatment was required. Mediastinoscopy was resumed, monitoring heart sounds through esophageal stethoscope, and compression of the innominate artery recurring on several occasions for 20 to 30-second intervals. A few minutes after the 1st incident, the pulse rate decreased from 80 to 85 to 45 to 50/minute. The blood pressure

*Attending Anesthesiologist.
†Attending Anesthesiologist.
‡White Plains Hospital, White Plains, New York 10601.

Paper received: 12/15/75
Accepted for publication: 2/13/76

was stable and no cardiac arrhythmias were observed. This severe bradycardia lasted for about 1.5 minutes and returned to a normal rate spontaneously. The postanesthetic course was uneventful. Mediastinal lymph nodes were seen to contain marked granulomatous change compatible with sarcoidosis.

DISCUSSION

The innominate artery may be compressed by the mediastinoscope, diminishing blood flow not only to the arm but, more importantly, to the brain through the right common carotid and vertebral arteries. We believe that judicious monitoring of carotid arterial blood flow is important with patients known to have significant arteriosclerotic disease of the carotid artery.

Transient left hemiparesis following mediastinoscopy have been reported.[3] Mediastinoscopy under local anesthesia[4] might be advantageous for patients with obstructive disease of the carotid artery, so that the patient's level of consciousness can be continuously evaluated. Use of the Doppler apparatus to monitor carotid blood flow might offer further advantage.

In our case, production of simulated cardiac arrest was likely due to compression of the innominate artery (figure). The vagi and their branches may be mechanically stimulated, injured directly by sectioning or contusion, or injured indirectly by compression from hematoma or edema in surrounding tissues. The severe bradycardia was probably related to the transient mechanical stimulation of the vagus by the mediastinoscope. Since the vagus and cardiac nerves may be manipulated, the ECG should be continuously monitored during this procedure.

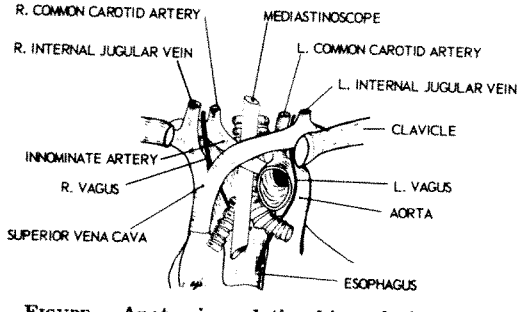


FIGURE. Anatomic relationships during mediastinoscopy.

The esophagus lies posterior to the trachea and usually is not in the mediastinoscopic area of dissection except in the subcarinal region, where it may be vulnerable. Laceration of major vessels in the superior mediastinum is also possible. The mediastinal pleura, particularly on the right side, lies close to the trachea and the pleural space can be entered inadvertently. Other complications include death after biopsy of pulmonary and innominate arteries, superior vena cava and azygos vein, in addition to injury of the vagus and recurrent laryngeal nerve, air embolism, tumor invasion of the suprasternal wound, subcutaneous emphysema, and cardiac arrhythmias due to inadvertent cardiac biopsy.[5]

One should constantly monitor the right radial pulse, since vigorous anterior retraction on the mediastinoscope will occasionally compress the innominate artery. Monitoring of arterial pressure of the right arm and heart sounds through an esophageal or precordial stethoscope is also desirable, as is auscultation of the chest for breath sounds, and airway problems related to recurrent laryngeal nerve injuries should be observed postoperatively.

ACKNOWLEDGMENT

The authors are grateful to Dr. S. H. Ngai, Department of Anesthesiology, The Presbyterian Hospital, New York, for his helpful advice in the preparation of this manuscript.

REFERENCES

1. Carlens E: Mediastinoscopy. A method for inspection and tissue biopsy in the superior mediastinum. Dis Chest 36:342-352, 1959

2. Preciano MC, Duvall AJ, Koop SH: Mediastinoscopy. A review of 450 cases. Laryngoscope 83:1300-1310, 1973

3. Trinkle JK, Bryant LR, Hiller HJ: Mediastinoscopy. Experience with 300 consecutive cases. J Thorac Cardiovasc Surg 60:297-300, 1970

4. Morton JR, Guinn GA: Mediastinoscopy using local anesthesia. Am J Surg 122:696-698, 1971

5. Ashbaugh DG: Mediastinoscopy. Arch Surg 100:568-573, 1970

Anesthesia for Vanishing Lung Syndrome:
Report of a Case

NELSON ISENHOWER, MD*
ROY F. CUCCHIARA, MD†

A patient with severe bullous emphysema in whom one bulla occupied an entire hemithorax and shifted the mediastinum to the opposite side was anesthetized for bullectomy in a lateral thoracotomy position using an awake intubation with a Bryce-Smith double-lumen endotracheal tube under spontaneous ventilation on room air. The maintenance anesthetic was halothane and oxygen, with pancuronium bromide for relaxation and ventilation of the good lung only. This technique avoids many of the potential problems presented by this type of patient.

INTRODUCTION

CHRONIC obstructive pulmonary disease (COPD), the most common chronic lung disease, presents many problems to the anesthesiologist.[1,2] A Hospital Records survey revealed that 22% (175,000) of the emphysematous patients discharged in 1974 had undergone surgery.[3]

We wish to describe an emphysematous patient who developed a bullous lesion so large that it completely filled the right hemithorax without causing a pneumothorax (vanishing lung syndrome). The patient's respiratory function was so impaired that operative resection of the lesion was required.

CASE REPORT

A 52-year-old known emphysematous male was referred for evaluation of dyspnea on minimal exertion and a "right pneumothorax" on chest roentgenogram. His chest films at admission, however, showed a large bulla covering almost the entire right thorax, with the right lung compressed and a left shift of the mediastinum. Physical examination at admission revealed a slender Negro male in moderate respiratory distress at rest, with a tracheal tug and intercostal retractions, increased anteroposterior diameter of the chest wall, and jugular venous distention to 45°. Breath sounds were absent on the right side and decreased on the left. He was treated with low-flow oxygen and antibiotics while being evaluated.

Pulmonary function tests (Table 1) were interpreted as showing a severe obstructive defect with hyperinflation. Arterial blood gases revealed hypoxemia with carbon dioxide retention (room air: pH 7.41, Po_2 52 mm Hg, Pco_2 55 mm Hg). When low-flow oxygen was administered (2 liters/min), he showed an even greater retention of carbon dioxide (pH 7.34, Po_2 71 mm Hg, Pco_2 64 mm Hg). Pulmonary arteriogram revealed pronounced bullous changes in the right upper lung field extending across the midline and severe compression of the right pulmonary artery vessels to the lower portion of the right hemithorax. Pulmonary hypertension was also noted. A xenon ventilation-perfusion scan showed a large ventilation defect of the right lung.

On the 10th hospital day, the patient underwent right bullectomy through a right lateral thoracotomy. The patient received

*Resident in Anesthesiology, Walter Reed Army Medical Center, Washington, D.C.
†Assistant Professor of Anesthesiology, Mayo Medical School, Rochester, Minnesota.
Paper received: 1/6/76
Accepted for publication: 2/27/76

TABLE

Results of Pulmonary Function Tests Before and After Resection of Large Bullous Lesion

	Before operation		After operation		6-Week follow-up	
	Value	% Predicted	Value	% Predicted	Value	% Predicted
MMEF	0.4 L/s	11	0.8 L/s	22	0.8 L/s	23
$FEV_{1.0}$	610 ml	20	1,060 ml	35	1,470 ml	49
VC	1,050 ml	27	1,810 ml	46	2,350 ml	60
FRC	2,570 ml	92	2,830 ml	102	3,060 ml	110
RV	2,330 ml	149	2,120 ml	136	2,080 ml	133
TLC	3,380 ml	61	3,930 ml	71	4,430 ml	80

no preoperative medication. A central venous pressure catheter, arterial catheter, electrocardiogram, and Foley catheter were used for monitoring. After diazepam 5 mg was intravenously administered, bilateral superior laryngeal nerve blocks were performed with 1% lidocaine, and topical anesthesia of mouth and pharynx was accomplished with 2 cc of 4% cocaine. A 6.5-mm, Bryce-Smith double-lumen endotracheal tube was inserted while the patient was awake and spontaneously ventilating with room air. The cuff to the left lung was inflated, and positive-pressure ventilation was begun to the left lung only. The lumen to the right lung was left open to room air. Induction was accomplished with thiopental, and relaxation was accomplished with pancuronium bromide. Anesthesia was maintained with halothane, oxygen, and controlled ventilation. Arterial blood gas values were satisfactory in the supine and left lateral positions.

The thorax was opened. The right lung was noted to be compressed, and one large bulla occupied approximately 95% of the hemithorax. The surgeon was unable to express air from the bulla. Ventilation of both lungs with equal pressure was then attempted, and nearly the entire tidal volume appeared to enter the bulla in the right upper lobe. Bullectomy was performed. Several smaller (3-cm) bullae were noted and also removed. The right lung was expanded. Intercostal nerve blocks were performed with 0.25% bupivacaine. Anterior and posterior chest tubes were inserted. The double-lumen endotracheal tube was replaced by an oral, 8.0-mm, Portex endotracheal tube with a low-pressure cuff. The patient was taken to the recovery room and placed on a volume ventilator (Bennett MA-1). A 600 to 800 ml leak per breath via the chest tubes was noted.

On the first postoperative day, paravertebral blocks were performed. The right lung gradually filled the entire right side of the chest. On the second post-operative day, the patient was weaned by intermittent mandatory ventilation and the endotracheal tube was removed. The patient continued to do well, and on the fourth postoperative day, the posterior chest tube was removed. The air leak gradually decreased, and the second chest tube was removed on the eighth postoperative day.

Postoperative pulmonary function tests showed improvement (Table 1). Arterial blood gases on room air revealed a pH 7.39, Po_2 64 mm Hg, Pco_2 40 mm Hg. The patient noted much improvement in his activity tolerance and was dismissed on the 12th postoperative day. He was both objectively and subjectively greatly improved and returned to work. Pulmonary function tests six weeks after the operation showed little further improvement (Table 1).

DISCUSSION

The patient with COPD presents several different problems to the anesthesiologist.[4] The problems that this patient exemplifies were related to three major areas: positive-pressure ventilation, oxygenation, and anesthetic management.

In bullous emphysema, when one bulla is very large while other bullae are small, Laplace's law relating to the expanding force in a hollow structure to the cross-sectional area applies. Laplace's law (when the thickness of the wall of the sphere is assumed to be negligible in comparison with the radius of curvature) could be stated as: the pressure within a bulla equals two times the wall tension of the bulla divided by the radius of the bulla.

If positive pressure is applied to the airway (that is, by way of an anesthesia bag), the large bleb tends to increase in size even more.[5-7] This increase could rupture the wall and cause a pneumothorax, and in this case, probably a tension pneumothorax. In a patient with marginal pulmonary and cardiovascular status, the results could be devastating.[8] A second consideration is that, even if a tension pneumothorax did not occur, the large bulla could allow most, if not all, of the tidal volume to enter its cavity. The increase in size of the bulla could shift the mediastinum, compress the good lung, and allow more of each succeeding tidal volume to enter the bulla. However, if a pneumothorax would occur and the patient could be treated with a chest tube of large bore, a large bronchial-cutaneous fistula could be created, and this could divert the entire tidal volume into the chest tube.

Like many patients with COPD this patient demonstrated that his drive to breathe was based on hypoxia and not on hypercapnia. A high inspired F_{IO_2} in our patient might have removed his only drive to spontaneous ventilation. This patient's oxygenation problems were compounded because, not only did he have decreased function of lung tissue but he also was effectively ventilating only one functioning lung.

Because of this patient's decreased pulmonary reserve, premedication was omitted before his arrival to the operating room. In order to ensure that no positive pressure would be applied to the airway, an awake intubation was chosen under spontaneous ventilation. A double-lumen endotracheal tube (left Bryce-Smith) was chosen firstly, to ensure that no positive pressure would be applied to the bulla and, thus, prevent ventilating only the bulla or causing a pneumothorax, and secondly, that ventilation could be guaranteed to the good lung, even in the presence of a possible bronchial-cutaneous fistula. The lumen to the right lung was left open to prevent any increase in pressure which might be caused by expansion of the partially compressed left lung.

Oxygen was added only after an airway was assured and positive pressure could be applied to the lungs independently. Halothane was chosen so that a high F_{IO_2} could be delivered, as this may be needed for any patient in the lateral thoracotomy position and especially in one who has decreased pulmonary function. As in any patient with a ventilatory defect, the uptake of an inhalation agent may be decreased somewhat owing to the $\dot{V}/\dot{Q}$ abnormalities present. The use of nitrous oxide in the presence of an air-filled body cavity must be very judicious.[9] Nitrous oxide was avoided because of its probable diffusion into the bulla, thus increasing its size, and because the nitrous oxide would decrease the inspired oxygen concentration.

During the surgery, it became obvious that several of the theoretic complications were no longer theoretic. By avoiding positive pressure, hyperinflation of the bulla on induction was avoided. After the chest was opened, both lungs were ventilated with equal pressure. Almost the entire tidal volume was displaced into the bulla, and adequate ventilation could not be maintained. By utilization of the double-lumen tube the ventilation could be directed away from the bulla and into the better lung. The ability to inflate or rest the poor lung was helpful to the surgeons in locating and isolating other resectable bullous areas.

REFERENCES

1. Tarhan S, Moffitt EA, Sessler AD, et al: Risk of anesthesia and surgery in patients with chronic bronchitis and chronic obstructive pulmonary disease. Surgery 74:720-726, 1973

2. Gold MI, Joseph SI: Bilateral tension pneumothorax following induction of anesthesia in two patients with chronic obstructive airway disease. Anesthesiology 38:93-96, 1973

3. Joint Study by Commission on Professional and Hospital Activities and IMS America Ltd., Amber, Pennsylvania, 1974

4. Katz J, Kadis L: Anesthesia and Uncommon Diseases. W B Saunders Co., Philadelphia, pp 199-201, 1973

5. Ting EY, Klopstock R, Lyons HA: Mechanical properties of pulmonary cysts and bullae. Am Rev Respir Dis 87:538-544, 1963

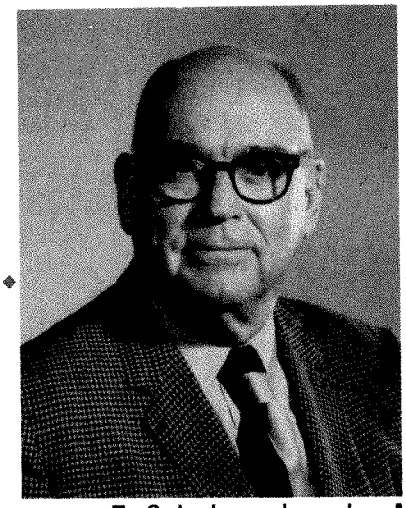
6. Macklin CC: Pneumothorax with massive collapse from experimental local over-inflation of the lung substance. Can Med Assoc J 36:414-420, 1937

7. Tinker J, Vandam L, Cohn LH: Tension lung cyst as a complication of postoperative positive pressure ventilation therapy. Chest 64:518-520, 1973

8. Martin JT, Patrick RT: Pneumothorax: its significance to the anesthesiologist. Anesth & Analg (Cleve) 39:420-429, 1960

9. Eger EI II, Saidman LJ: Hazards of nitrous oxide anesthesia with bowel obstruction and pneumothorax. Anesthesiology 26:61-66, 1965

We Salute . . . .



Lawrence F. Schuhmacher, Jr., M.D.

FREQUENTLY, superlatives are used to salute colleagues and to describe their accomplishments. In contrast, there are a unique few for whom superlatives somehow seem out of place, and who are more comfortably identified by their sincerity and qualities as real human beings. Dr. Lawrence F. Schuhmacher, Jr., Professor and Chairman of Anesthesiology at the Baylor College of Medicine, is truly one of these unique few.

Larry was born in Meade, Kansas, the oldest of three boys. During his youth and early adulthood, he and his brothers alternated between the summertime physical labors of a large wheat farm and the wintertime mental labors of school. In 1933, the trio graduated together from the University of Kansas, two physicians and an engineer.

Following graduation, Dr. Schuhmacher migrated from Kansas to New York City for an internship at the Fifth Avenue Hospital. During the year he met and married Florence M. Stout, an obstetrics supervisor. During the subsequent 5 years, Larry carried on a busy general practice in the Dust Bowl depression of Western Kansas. In 1940, the Schuhmachers again returned to the East Coast, where Larry served 2 years as an anesthesia resident at the Lahey Clinic in Boston. Immediately after training, Larry entered the Army. After a year in Iceland, his unit was transferred to England. Shortly after D-day, he was assigned to a Thoracic Surgical Center in the European Theater of Operations, where he remained until the end of World War II. He was a major at the time of his discharge and the recipient of the Bronze Star.

In 1945, Dr. Schuhmacher accepted the joint responsibilities of Professor and Chairman of the Department of Anesthesiology at the Baylor University College of Medicine and Director of Anesthesiology at the Hermann Hospital in Houston, Texas. There is little question that the Gulf Coast sunshine after the miserable damp-cold of the European winters may have influenced this move as much as the challenge of the rapidly developing Texas Medical Center.

Once relocated permanently in the South, Larry organized a formal residency program and actively promoted the growth of anesthesiology to parallel the growth of surgery

in Houston. Dr. Schuhmacher stepped down as Chairman of the Baylor program in 1953 but retained a Clinical Professorship in the Department until 1960. In 1969, he also resigned his responsibilities at the Hermann Hospital. This training program continues, however, and is now incorporated into the University of Texas Health Science Center at Houston.

After a brief but "active effort" at retirement, Dr. Schuhmacher came back to teaching and the operating room. He returned first to Hermann Hospital and then, on a part-time basis, to the Houston Veteran's Administration Hospital. In 1974, he accepted the appointment as Professor and Chairman of Anesthesiology at Baylor for the second time. On an almost daily basis, Larry can be found in the Fondren-Brown Cardiovascular Unit of The Methodist Hospital, caring for patients and imparting to trainees what he has learned on the basis of two careers in anesthesiology.

Despite his propensity for patient care, Larry finds time to enjoy the great outdoors. Frequently he is accompanied by Mrs. Schuhmacher when he is hunting or fishing, although with the recent sale of his boat, Florence lost her position as First Mate on excursions onto the Gulf of Mexico. The Schuhmachers' only child, Lawrence F. III ("Mike"), is an anesthesiologist practicing in San Antonio, and Larry's brother, Nelson R., is an anesthesiologist who has recently retired from practice in California.

Dr. Schuhmacher is a Diplomate of the American Board of Anesthesiology, a Fellow of the American College of Anesthesiologists, and a long-time supporter of the International Anesthesia Research Society. He has served as President of both the Houston Surgical Society and the Doctors' Club of Houston and was an ASA Director for 9 years.

It is with pleasure that we salute Lawrence F. Schuhmacher, Jr., M.D., a colleague and friend who has devoted his professional lifetime to our specialty.

SHOCK LUNG. Shock lung syndrome follows profound hypotensive episodes secondary to hemorrhage or sepsis and is associated with a 60 to 90 percent mortality. The present study sought to determine the efficacy of pharmacologic doses of steroids in the treatment of this syndrome. Ten patients with the diagnosis of shock lung syndrome were treated with methylprednisolone 30 mg/kg intravenously every 6 hours. All patients were mechanically ventilated and positive end expiratory pressure (PEEP) was necessary in 5 patients. There was a progressive increase in arterial oxygenation and resolution of pulmonary edema that was not influenced by PEEP. Nine patients survived and one died from disseminated intravascular coagulation. The author concludes that methylprednisolone improved survival in patients developing shock lung syndrome. *(Sladen A: Methylprednisolone. Pharmacologic doses in shock lung syndrome. J Thorac Cardiovas Surg 71:800-806, 1976)*

Correspondence

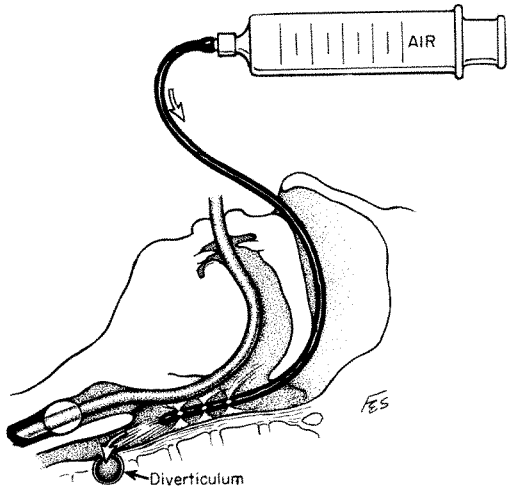
PLASTIC-COVERED WIRE STYLET

To the Editor:

I read with interest Dr. Morris J. Nicholson's article on a plastic-covered solid copper wire stylet, which appeared in *Anesthesia and Analgesia* (55:150, 1976). This brought back memories.

On several occasions, pieces of plastic on our stylets would be sheared off and left in the patient's tracheobronchial tree. I wondered if the plastic covering on the new TW (thermoplastic, weatherproof) copper wire described by Dr. Nicholson would also shear. I inserted the TW coated wire through 2 randomly selected metal endotracheal tube connectors, made a kink in the wire, and then pulled the stylet out of the endotracheal connector. The results—a partially sheared-off piece of plastic (figure).

No doubt Dr. Nicholson's material is superior to that which I used many years ago; however, I wonder if a warning should be included that the possibility of shearing some of the coating still exists. I am sure that the chances of this plastic covering being sheared while using plastic endotracheal tube connectors would be almost nil.



The stylet described by Dr. Nicholson is an improvement over other forms of coated-wire stylets and I plan to replace the spiral-wire stylets because of the distinct advantages of these plastic-covered stylets.

Charles J. Restall, MD
Department of Anesthesiology
Mayo Clinic
Rochester, Minnesota

* * *

To the Editor:

Dr. Restall raises a very important question concerning the safety of the plastic-covered solid copper wire (#12) stylet which I described. To date we have not been aware of this complication occurring in our practice. Recently, I have tried to reproduce the shearing effect described by Dr. Restall when he pulled a kinked stylet through a metal endotracheal tube connector; however, I had the metal connector inserted in an endotracheal tube as it would be used in clinical practice. Even when the tube and stylet were bent at a 90° angle or greater, I was not able to produce any shearing of the plastic coating. Nevertheless, this is an important consideration which must be constantly kept in mind and for which these stylets should be examined after each use.

If any of our readers have experienced this complication (a piece of the sheared plastic coating remaining in the tracheobronchial tree), I would greatly appreciate hearing from them.

Morris J. Nicholson, MD
Department of Anesthesiology
Lahey Clinic
Boston, Massachusetts

In each issue of the Journal an article of particular interest and value to anesthesiologists, which has been published elsewhere, will be presented. Primarily the material will contain fundamental basic information which has been presented by anesthesiologists, physiologists, pharmacologists, and others and, on occasion, by commercial firms. In the last instance, these reprintings are not to be construed as an endorsement of the particular commercial firm or its product by Anesthesia and Analgesia—Current Researches.

Attorney Urges Study of Doctors' Professional Relationships

E. BLAKE MOORE
Spears, Moore, Rebman & Williams
Law Offices
Chattanooga, Tennessee

E. Blake Moore delivered the following address at a meeting of the Tennessee Valley Medical Association in 1975. Among the audience were a number of doctors whom Moore has defended in medical malpractice suits. Moore speaks candidly and gets directly at the heart of a fundamental issue in the malpractice situation. That is, doctors' relationships—with their patients, with other doctors, and with lawyers.

A GOOD bit of my professional life has been dedicated to the defense of medical malpractice claims. It is something I like to do. Defending you is a challenging and personally satisfying part of my work. In short, I like you people and would like to be put in the category of friend, not foe.

I say this introduction because I want to talk to you in a way that might be acceptable to you only if you keep it firmly in your mind that I really am on your side.

My topic is an effort to demonstrate some of the common sense, simple things that go so far to make you good doctors and good people—and, therefore, believe it or not, "immune" from claims of malpractice. So, what are some of these simple things?

Let's start with the most obvious—your relationship (or lack of one) with your patients. Isn't it strange that the person who first comes to you in complete confidence, fully prepared to refer to you fondly as "my doctor," is the very same person who sues the heck out of you?

Quite obviously, somewhere along the line, something went wrong to cause such a wonderful start in a mutually beneficial relationship to end up fraught with suspicion, frustration and anger.

It's right here—in the midst of your relationship with your patient that most of the malpractice cases get started.

You can blame anyone or anything you want—the law, lawyers, courts, juries, insurance companies, or the changing times. But if you don't examine yourself, your patient and how the two of you are doing in your human relationship, you will be putting the

Reprinted with permission from MALPRACTICE DIGEST and the author.

blame in the wrong place. Moreover, you will be ignoring a major cause of malpractice litigation and you will be contributing to making the situation worse.

As you look at yourself and your patients, do you see how you are isolating yourself from your patient? Do you have one of those offices where the patients are herded into a corral, often called a "waiting room," or out into the hall?

Is your office built so that a great wall separates all "your people" from "them?" (Oh, yes, I know you cut a hole through which one can talk and hand money). Those walls are terrible mistakes.

Have you got a "front line" of women whose only goal in life is to protect you from your patients? Do you take time to find out if those front line ladies are as nice to your patients as they are to you? Do you realize how much harm is done by the women who "man" the wall? Do your patients wait for hours, even 30 minutes, to have a few precious moments of your time? Are you oblivious to the value of your patients' time?

Do you enjoy your work and your patients or, is your practice more like a production line with quotas to make?

What caused you to become a doctor in the first place? What impels you in your practice? Is it a genuine interest in serving mankind or is it the profit potential? Do you place financial considerations above the physical or emotional needs of your patients?

Have you "had to" develop a good many hard-headed business practices as part of your handling of your patients? Has your idealism been replaced by "practical business considerations?"

Are you job-oriented? That is, do you attempt to serve your patients by a cold purely scientific approach wherein the patient is merely another case, a detached problem, to be solved and disposed of? Do you have the attitude that you should refuse to be led around by the nose by your patients? And, the companion attitude—that you must train your patients to adhere to your schedules and patterns of life—indeed even to timing their illnesses?

Do you or "your people" at the wall indulge in untruthful representations that you are "in surgery" or "had an emergency" when the truth is you are lingering over a cup of coffee—or some other personal matter? Are you willing to listen to your patients about non-medical factors which may bear upon the patient's illness?

Do you get out in the world—the non-doctor world—or do you go to doctor meetings, doctor luncheons, doctor social events, doctors' homes, and, when you play golf, it's in the "doctor dog fight?". Do people get to know you in places and circumstances far removed from your doctor's office?—like school work, church work, Boy Scouts, Clubs, social gatherings where there may not be any other doctors, etc.?

O.K., enough is enough! But I hope the point is made—that you may be making a lot of mistakes in your relationships with your patients, and other members of the outside world. It is a situation that needs attention. For instance, it doesn't take much imagination to visualize what is happening when these relational mistakes are being made thousands of times a day in almost every doctor's office.

We are seeing the practice of medicine, more and more, as an impersonal, scientific, sterile, unpleasant business. More and more a doctor's office is like a computer into which we are fed—rather than a place of warmth and tender loving care.

Solve some of these relational problems, and you will see a real minimizing of malpractice claims.

While we're talking straight I'd like to say something about "The Conspiracy"—the conspiracy of silence that alleges that no doctor will testify against another doctor simply because he's a doctor.

First, I don't believe there is such a thing. In my experience, I've seen many doctors ready to testify against their colleagues.

Second, of course, it is wrong to "conspire" against anyone in the way "The Conspiracy" makes it sound.

Third, there may be a lot of good considerations that went into a doctor's decision not to testify. It often meant a recognition that very few medical problems are either black or white. It recognizes that a lot of what you do is a matter of judgment and that someone else's way of practicing medicine may be as good as yours. It recognizes your own capacity to be wrong and an interdependence among all doctors—the

general practitioner and the specialist as partners in a mutual endeavor. So, only to the extent that "The Conspirary" made you think and act along these lines, I wish it would make a comeback.

Along this line, we ought to mention how your relationships with each other have deteriorated—resulting in too much criticism and "loose talk." How often are the seeds of suspicion sown by the raised eyebrow, evasive answer, or sarcastic or critical remarks of the doctor who next sees the patient? How many times have petty personality conflicts given rise to unwarranted criticism? How often does a jurisdictional dispute between two warring specialty groups give the patient cause to wonder if he was mistreated? What you do to each other is awful! One is reminded of 2 or 3 old expressions:

1. "Loose lips sink ships"—and doctors.

2. "Who needs enemies with friends like these?"

3. "Button your lip."

One other point I would like to discuss is the antagonism that too often exists between your profession and mine.

You very often see attorneys as the real enemy—not the patient. You resent the ways of attorneys and fear whatever it is that goes on in the court room.

Your tendency toward isolation may be one reason for this resentment but there may be another—it may stem from the different (really opposite) ways that we in the two professions go about solving problems. Our training and practice have a basic difference.

We lawyers are trained in a curriculum that is essentially a continuing Socratic dialogue, whereas you doctors are instructed in a method that is largely doctrinal and authoritative. The lawyer's meat is controversy and he functions in the adversary system wherein each side takes its best shot before an impartial tribunal that decides what is "right." The doctor, on the other hand, is conditioned to objective scientific inquiry. To a doctor, notorious contest is disruptive and has no place in the search for solutions.

The lawyer, typically, sees a challenge in open dispute, whereas the doctor may see it only as an unnecessary insult.

We attorneys live in controversy and are constantly aware of the other person's point of view and possible criticism. We spend a lot of time as the "Devil's Advocate"—not a reference to your disgruntled patient and his attorney.

As a doctor, you are not prepared for criticism of how you practice medicine. Your status has been only a "Little Less Than God." You give orders all day long and seldom take any. You are the protector of our health and well-being. Most of the public still treats you with a certain reverence.

So, it's not at all surprising that you would have a problem with criticism, depreciation or attack. Very little, if anything, has prepared you for it.

We, in two professions, then, have two essentially different professional lifestyles—two approaches to problem solving. Neither is wrong. Both are time-tested. Both are working rather well.

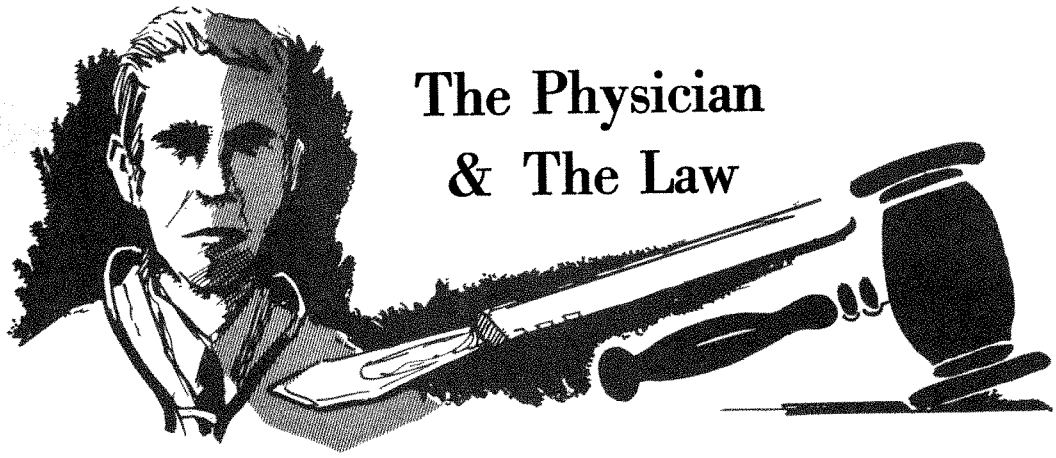
What neither profession has had, in surplus, is a good understanding of each other.

So, my summation and plea is:

(1) Take a hard look at yourself as a doctor and your relationship with each patient.

(2) Take a hard look at yourselves, not as individual superstars, but as a *group* of professional people with no real reason to exist, except to work together—to bring as much good health and happiness to your patients as possible.

(3) Take a good open-minded look at the legal profession, and the system within which it works, and your relation to it.



No Liability for Death of Patient During Anesthesia

A TRIAL court properly rendered a verdict in favor of several physicians, an anesthetist, and a hospital in a negligence suit, a Texas appellate court ruled.

A patient died of a cardiac arrest while undergoing anesthesia before surgery to repair a diaphragmatic hernia. Her husband brought the negligence suit against the physicians, the anesthetist, and the hospital. A trial court ruled that they were not liable. Appeals were eventually taken to the state supreme court, which remanded the case for a new trial. After a retrial, the jury again refused to find negligence.

On appeal, this trial court's decision was affirmed. The appellate court overruled several points of error in reaching its decision. A written consent to surgery signed by the patient was properly admitted into evidence, the court said. Medical textbooks not recognized by the testifying experts were properly excluded by the court as hearsay.

The appellate court also said that the manufacturer's recommendation of flow rate for anesthesia equipment could not be used to establish a medical standard to determine whether the anesthetist was negligent in using a different flow rate.

The decision in favor of the physicians, anesthetist, and hospital was affirmed.—*Webb v. Jorns*, 530 S.W.2d 847 (Tex. Ct. of Civil App., Oct. 10, 1975; rehearings denied, Nov. 21, 1975 and Dec. 19, 1975).

Editor's Note: Prior decisions in this case were reported in THE CITATION, Vol. 24, No. 10, p. 146 and Vol. 27, No. 2, p. 26.

Reprinted by permission from THE CITATION, published by the Law Division of the American Medical Association.

Questions and Answers

We invite you to submit questions to the Editorial Office, Kahler East, Suite C, Rochester, Minnesota 55901. The names of those submitting questions will remain anonymous if so desired.

The answers will be prepared by competent authorities, and their names will or will not appear, according to their specific wishes.

Ronald W. Dunbar, M.D.
Contributing Editor
Atlanta, Georgia

* * *

QUESTION: *A healthy 22-year-old married but (planned) childless operating-room nurse, who has worked full time in the operating room for the past 6 months and is aware of the harmful effects of waste anesthetic gases on parturients, desires to start a family. She asks: "Should I quit working in the operating room and wait a specific length of time before getting pregnant? If so, how long? Should I wait until I am pregnant and then quit? If so, how long after I become pregnant could I safely work in the operating room?"*

MD, Tennessee

ANSWER: This young operating-room (OR) nurse asks very pertinent questions with respect to her planned pregnancy and continued work in the OR. Unfortunately, there are little firm data with which to answer her. Hopefully, additional information will be available following completion of the second phase of the National Study on the Effects of Trace Anesthetic Agents on the Health of Operating Room Personnel. At that time, a comparison of health experience before and after the installation of scavenging equipment will be possible. This should allow an estimate of the time factors involved in the pregnancy-exposure hazard.

Although a relationship between these health hazards and OR exposure has been established by the National Study, a cause-effect response to the anesthetic gases remains to be confirmed in man. There are, however, consistent animal data to establish this possibility.

From a practical point of view, and on the assumption that anesthetic gases are causal, the important consideration is whether this individual has been working in a scavenged OR. Efficient scavenging systems remove 90 to 95% of the anesthetic gases formerly present. Since in the experimental animal the concentrations producing fetal resorptions are at least a factor of 10 away from those trace anesthetic-gas concentrations present in a scavenged OR, one may presume that scavenging offers a reasonable degree of safety.

In view of the increased incidence of congenital abnormality in the children of exposed OR personnel, one might be especially cautious with the woman who is in an increased risk category. Thus, a family history of congenital abnormality might suggest the importance of the added precaution of her removal from the OR several months prior to and during the first trimester of pregnancy. The advisability of such a move for the normal individual working in a scavenged OR is debatable. Thus, if our nurse has no positive family history, our recommendation would be for her to continue her work, but make certain that anesthetic gas scavenging is efficiently practiced.

Ellis N. Cohen, MD
Department of Anesthesiology
Stanford University Medical Center
Stanford, California

* * *

QUESTION: *I am not a purist, but as a physician brought up (in Canada) to respect the nuances of the King's (or Queen's) English, I am puzzled by the frequent encounters in "the literature" with* metabolism *used as a synonym for* destruction *or* biodegradability. *I was taught that metabolism is a function of a living organism. I*

can find no authority (Oxford English Dictionary, Oxford International Dictionary, Merriam-Webster International, Stedman's Medical Dictionary, Dorland's Medical Dictionary) that recognizes substitution of metabolism *for* catabolism *when meaning the degradation of an inorganic drug or other product. I would appreciate the opinion of your editorial associates.*

MD, Toronto

ANSWER #1: According to Stedman's Medical Dictionary (22nd edition, 1972), "Metabolism . . . consists of anabolism, or those energy consuming processes that convert small molecules into large (eg, amino acids to proteins), and catabolism, or those energy producing processes that convert large molecules into small (eg, glycogen to pyruvic acid)." Consequently, the questioner is right, as far as being a purist, in that metabolism refers to both the processes involved in the synthesis of tissue and in the processes involved in the breakdown or degradation of tissue. However, when one is talking about biodegradation of a drug, obviously, the use of metabolism refers to the subdivision of catabolism rather than the subdivision of anabolism. I would think that the substitution of this word for the other word is not something that should seriously interfere with the reader's understanding of the published articles on the subject.

Robert G. Merin, MD
Department of Anesthesia
University of Rochester Medical School
Rochester, New York

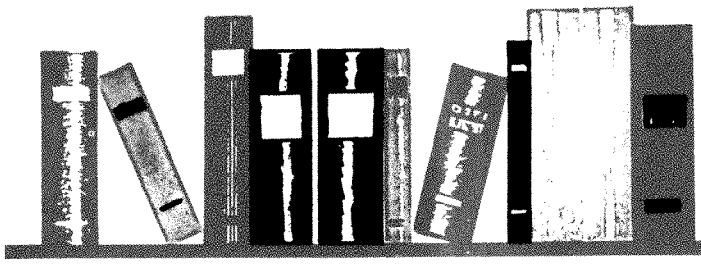
* * *

ANSWER #2: The term metabolism has come to mean the sum total of all the enzymatic reactions that occur in an organism. This definition, while very general, would include the obtaining of chemical energy for the needs of the cell, as occurs when the endogenous or nutrient chemicals are broken down, the conversion of nutrient chemicals from one form to another, and the synthesis of larger molecules such as proteins, etc, from the smaller endogenous or nutrient chemicals. Thus, metabolism includes both *anabolism*, which means the synthesis of a larger molecule from smaller components, and *catabolism*, meaning the breakdown of a larger molecule into smaller parts. This is easily understandable in terms of endogenous and nutrient chemicals, but in recent years the term metabolism has been expanded to include the metabolism of foreign chemicals, including drugs.

It is true that in many instances the term metabolism has been used to mean the breakdown or catabolism of a compound, and this is still within the definition of metabolism, since catabolism is a part of metabolism. In addition, many drugs or foreign chemicals that enter the biologic system also undergo an increase in size of molecule by conjugation of one type or another; thus, drug metabolism involves anabolism as well. It is not important what size the final product of drug metabolism is, the important consideration is that it loses its biologic activity and this can be accomplished in some cases by catabolism and in some by anabolism. Thus, the term "degradation" may refer as much to loss of biologic activity as to size of molecule.

Therefore, the term metabolism is appropriate when referring to the enzymatic transformations undergone by foreign chemicals or drugs as well as nutrient chemicals, because it covers, generally, all such transformations of these chemicals, whether by degradation or enlargement of the molecule.

Russell A. Van Dyke, PhD
Department of Anesthesiology
Mayo Clinic
Rochester, Minnesota



the book shelf

Oxygen Measurements in Biology and Medicine—Edited by J. P. Payne, MB, ChB, DA, FFARCS, and D. W. Hill, MSc, PhD, FInstP, FIEE, London, Butterworths, 1975, 415 pp.

This book consists of a series of presentations by a select group of workers and investigators. Although it hardly represents an up-to-the-minute definition of the "state of the art," it does provide the clinician with an overview of the major problems associated with oxygen measurement and the directions various researchers are taking toward solutions.

The first session of the symposium deals with some of the intricacies of oxygen transport and presumes a fairly detailed knowledge of the subject on the part of the reader. The subsequent seven sessions deal with various items of hardware used in oxygen measurements, along with a clear statement, in most instances, of the advantages and shortcomings of each. Each session is followed by a transcript of the discussion of the previous papers by the symposium participants. These exchanges are interesting and entertaining, since the editor has preserved the feelings of enthusiasm, doubt, sarcasm, and respect characteristic of such free-flowing, spontaneous discussion among experts.

Even though the volume does not qualify entirely as a reference work, it is sufficiently complete to provide the reader with a good idea of where we are in oxygen measurement and where we are likely to go.

Edward P. Didier, MD
Department of Anesthesiology
Mayo Clinic
Rochester, Minnesota

Childbirth, A Joy—Not Suffering—Abouleish, Ezzat, M.D., Philadelphia, Dorrance & Company, 1975, 110 pages, price $2.95.

This little book was written by Dr. Abouleish to describe to the expectant mother the various methods of obstetric anesthesia. The terminology is simple and allows a layperson to understand the book easily and to read it in a short period of time. Most of the chapters are presented in question-and-answer format. Many of the questions most frequently asked by women are answered. Fears and misconceptions about anesthesia are handled well by the author.

The book briefly discusses physiologic changes during pregnancy, stages of labor, and the anatomy involved in parturition. The psychology and physiology of pain during childbirth are discussed, as is the supportive role of the father. Types of anesthesia described include paracervical, pudendal, spinal, epidural, and caudal block, as well as general anesthesia and analgesia. The advantages and disadvantages of each type of anesthetic procedure are compared. Also included are short chapters on natural childbirth and on hypnosis and acupuncture for the control of pain. Anesthesia and indications for cesarean section are discussed.

While epidural block is discussed well and is obviously the preference of Dr. Abouleish for childbirth, he also clearly points out that no one method of analgesia is good for all parturients under all circumstances.

Rick S. Schwettmann, M.D.
Department of Anesthesiology
Mayo Clinic
Rochester, Minnesota

IN THE NEXT ISSUE

Scientific Articles

Nov.-Dec., 1976

ENFLURANE AS A PRIMARY ANESTHETIC AGENT FOR PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE—Rene Rodriguez, M.D., and Martin I. Gold, M.D., Miami, Florida.

POSTPARTUM HYPERTENSION AND CONVULSION AFTER OXYTOCIC DRUGS—Ezzat Abouleish, M.B., B.Ch., M.D., Pittsburgh, Pennsylvania.

ISOENZYMES OF CREATINE PHOSPHOKINASE IN SERUM OF FAMILIES WITH MALIGNANT HYPERPYREXIA—Herbert Y. Meltzer, M.D., Shakeela Z. Hassan, M.D., Paul Russo, and Hyong Won Cho, Ph.D., Chicago, Illinois.

UNEXPECTED HEPATIC DYSFUNCTION FOUND BY MULTIPLE LABORATORY SCREENING—William H. Schemel, M.D., Buffalo, New York.

A SIMPLE TECHNIC TO MINIMIZE TRACHEAL ASPIRATION—Roy F. Cucchiara, M.D., Rochester, Minnesota.

COMPARISON OF DOT TEST AND DIGIT-SYMBOL TEST FOR STREET FITNESS OF OUTPATIENTS—Joseph G. Ritter, M.D., and Nancy Anderson, M.A., Blue Bell, Pennsylvania.

THE ANESTHETIC POTENCY OF LIDOCAINE IN THE RAT—Cosmo A. DiFazio, M.D., Ph.D., James Niederlehner, M.D., and Robert G. Burney, M.D., Charlottesville, Virginia.

ARTERIAL AND VENOUS PLASMA LEVELS OF BUPIVACAINE FOLLOWING PERIPHERAL NERVE BLOCKS—Daniel C. Moore, M.D., L. E. Mather, M.D., L. Donald Bridenbaugh, M.D., D. F. Lysons, M.D., and W. G. Horton, M.D., Seattle, Washington.

CEREBROSPINAL FLUID PRESSURE DURING PNEUMOENCEPHALOGRAPHY AND NITROUS OXIDE INHALATION—William L. Paul, M.D., Edwin S. Munson, M.D., and Jack E. Maniscalco, M.D., Gainesville, Florida.

THE ANESTHETIC EFFECT OF OXYGEN—Raymond A. Smith, D.Phil., and W. D. M. Paton, D.M., F.R.S., F.R.C.P., San Francisco, California and Oxford, England.

RATIONAL CHOICE OF LOCAL ANESTHETICS FOR OBSTETRICAL ANESTHESIA—Larry Salts, M.D., Mary Ann Ott, M.S., and Philip D. Walson, M.D., Tucson, Arizona.

CARDIOVASCULAR EFFECTS OF LIDOCAINE DURING ACID-BASE IMBALANCE—Ronald W. Yakaitis, M.D., John D. Thomas, M.D., and John E. Mahaffey, M.D., Charlestown, South Carolina.

OBSTETRIC ANESTHESIA TRAINING CENTERS IN THE U.S.A.—James S. Hicks, M.D., Gershon Levinson, M.D., and Sol M. Shnider, M.D., San Francisco, California.

UPTAKE AND EXCRETION OF 1-BROMO-1,2,2-TRIFLUOROCYCLOBUTANE IN MAN: COMPARATIVE STUDY ON PHARMACOKINETICS AND METABOLISM OF INHALATION AND ANESTHETICS—Duncan A. Holaday, M.D., and Vera Fiserova-Bergerova, Ph.D., Miami, Florida.

NALOXONE ANTAGONISM AFTER NARCOTIC SUPPLEMENTED ANESTHESIA—Benjamin J. Kripke, M.D., Albert J. Finck, M.D., Narendra K. Shah, M.D., and John C. Snow, M.D., Boston, Massachusetts.

THE EFFECTS OF STELLATE GANGLION BLOCK ON THE IDIOPATHIC PROLONGATION OF THE Q-T INTERVAL WITH CARDIAC ARRHYTHMIA (THE ROMANO-WARD SYNDROME)—Hisashi Yanagida, M.D., Judo Higo, M.D., and Chiyuki Kemi, M.D., Tokyo and Yokohama, Japan.

ANESTHESIA AND THE MODIFICATION OF RESPONSE TO INFECTION IN MICE—Peter G. Duncan, M.D., Bruce F. Cullen. M.D., and Nancy N. Pearsall, Ph.D., Seattle, Washington.

KETAMINE AND INTRAOCULAR PRESSURE IN CHILDREN—Baiba Ausinsch, M.D., Robert L. Rayburn, M.D., Edwin S. Munson, M.D., and Norman S. Levy, M.D., Ph.D., Gainesville, Florida.

THOUGHTS ABOUT MEDICAL WRITING—Charles G. Roland, M.D., Rochester, Minnesota.

COMPARISON OF TIDAL VOLUME LOSSES IN SEVERAL PEDIATRIC VENTILATORS WITH INCREASING AIRWAY PRESSURE—Robert E. Binda, Jr., M.D., David R. Cook, M.D., Carl G. Fischer, M.D., Pittsburgh, Pennsylvania.

THE DEVELOPMENT OF AN ACUTE TOLERANCE TO KETAMINE—James F. Cumming, M.D., Ph.D., Minneapolis, Minnesota.

LORAZEPAM PREMEDICATION: LACK OF RECALL AND RELIEF OF ANXIETY—Robert J. Fragen, M.D., and Nancy Caldwell, Chicago, Illinois.

CASE HISTORY #93

BRIEF REPORTS:

SUPINE HYPOTENSIVE SYNDROME CAUSED BY INTRA-ABDOMINAL MASS: A CASE REPORT—Jong Min Kim, M.D., Chana Buakham, M.D., and Florence McAmis, R.N., Kansas City, Kansas.

BRONCHIAL BLOCKADE IN A CHILD WITH BRONCHO-PLEURAL-CUTANEOUS FISTULA USING A "FOGARTY" BALLOON-TIPPED CATHETER—W. F. Cant, M.D., John H. Tinker, M.D., and Sait Tarhan, M.D., Rochester, Minnesota.

DECREASED ARTERIAL OXYGENATION DURING SODIUM NITROPRUSSIDE ADMINISTRATION FOR INTRAOPERATIVE HYPERTENSION—Joseph L. Seltzer, M.D., Joseph B. Doto, Jr., M.D., and Jay Jacoby, M.D., Ph.D., Philadelphia, Pennsylvania.

A METHOD FOR INSERTING THE CARDEN TUBE—James E. Cooke, M.D., Judith B. Hood, M.D., and John D. Thomas, M.D., Charleston, South Carolina.

AN ANESTHETIC GAS SCAVENGER FOR THE JACKSON-REES SYSTEM—Kenneth J. Cestone, M.D., William P. Ryan, C.R.N.A., and Charles D. Loving, R.N., Bennington, Vermont.

HUMIDITY OUTPUT OF THE COLUMBIA PEDIATRIC CIRCLE—Sivam Ramanathan, M.D., Jack Chalon, M.D., Peter Rand, and Herman Turndorf, M.D., New York, New York.

DIFFICULT EXTUBATION OF AN ENDOTRACHEAL TUBE CUFF—Thien Yew Ng, M.D., and Tapan D. Datta, M.D., Pittsburgh, Pennsylvania.

ACUTE MAXILLARY SINUSITIS COMPLICATING NASOTRACHEAL INTUBATION: A CASE REPORT—T. James Gallagher, M.D., and Joseph M. Civetta, M.D., Miami, Florida.

A Guide for Authors

Anesthesia and Analgesia . . . Current Researches invites manuscripts on subjects pertinent to the specialty of Anesthesia.

Send manuscripts and illustrations in *triplicate* to:

T. H. Seldon, MD, Editor
Kahler East, Suite C
Rochester, Minnesota 55901

Four categories of reports will be considered for publication.

1. Original articles describing clinical or laboratory research.

2. Brief Reports describing new anesthetic technics, equipment, clinical, or laboratory studies.

3. Case Reports.

4. Letters-to-the-Editor.

EDITORIAL POLICIES

Peer review.—All papers submitted are reviewed by selected referees with respect to validity, pertinence, completeness, and originality. If accepted for publication, editorial revisions may be made to aid clarity and understanding. Edited copy will be submitted to authors for approval before the paper goes to the printer. Pageproofs also will be submitted to the authors for final approval. Reprint order forms will accompany pageproofs.

Cover letter.—A letter must accompany each manuscript, stating that the work has not been simultaneously submitted to another journal or previously published in part or whole. The name and address of the author to whom correspondence may be directed should be given.

Legal and ethical considerations.—Information or illustrations which might permit identification of patients must not be used.

Reports describing data from experiments performed on humans must contain a statement in the Methods section, when appropriate, that written informed consent and/or institutional approval of the investigation has been obtained, and that procedures involving the use of animals was conducted so as to minimize discomfort.

Excerpts from material published elsewhere must be accompanied by written permission from the author and publisher to reproduce the material.

JOURNAL STYLE

Format.—All portions of the manuscript should be typewritten and double-spaced, including lists of reference citations. Each component of the paper (title page, with authors' academic rank and addresses, Introduction, Methods, Results, Discussion, References, Legends) should begin on a separate page. Original articles must be preceded by an Abstract concisely describing the purpose, methods, results, and conclusions. Abstracts should not exceed 1 typewritten page in length. Brief Reports and Case Reports do not require an Abstract, but a Summary at the end may be appropriate.

Original articles should be concise (not over 3000 words) and present new information pertinent to anesthesia. Preliminary reports or fragments of material that may better be included in a single, more detailed, report should not be submitted. Brief Reports describing new equipment or technics should present new advances, with advantages over the alternatives. Descriptions of new equipment must be sufficient to permit the reader to either construct or purchase the equipment. Case Reports should emphasize important clinical conditions or variations in typical patient responses. Letters-to-the-Editor must be brief (250-500 words) and should offer constructive comments on

recently published articles or discuss areas of general interest to anesthesiologists.

Measurement units.—The metric system should be used for all such data as length, mass, volume, and temperatures. Torr should be used in place of mm Hg for partial pressures. Authors are encouraged to adopt the International System of units (moles per liter rather than mg percent) for concentrations or amounts of substances. (See Padmore GRA, Nunn JF: SI Units in relation to anaesthesia. A review of the present position. Br J Anaesth 46:236-243, 1974).

Drug names.—Generic or chemical drug names are required. Brand names may be inserted in parentheses after the generic name, if pertinent.

Abbreviations.—The first time an abbreviation appears it should be preceded by the full word it represents.

Respiratory symbols.—Symbols for respiratory physiology should be defined the first time used and should follow Pappenheimer J et al: Standardization of definitions and symbols in respiratory physiology. Fed Proc 9:602-605, 1950.

References.—References should correspond to Index Medicus style and should be listed in the same numerical order as they appear in the text. Reports that are not accessible to all readers or that have not undergone editorial review (abstracts, correspondence, or personal communications) should not be included in numerical listings but may be footnoted. They should include pertinent addresses as well as source and authors' names.

Illustrations.—Drawings and photographs (unmounted glossy prints) should be numbered in order of appearance in the manuscript and labeled on the back with the first author's name and indicate the top edge of the picture.

Tables.—These should carry a title or caption and should supplement, not duplicate, the text.

51ST CONGRESS

International Anesthesia Research Society

MARCH 6-10, 1977

DIPLOMAT RESORT AND COUNTRY CLUBS
HOLLYWOOD, FLORIDA

Anesthesia and Analgesia CURRENT RESEARCHES

BACK ISSUES AVAILABLE

Available at $3.00 Per Issue

Vol.	Year	Numbers Available						Vol.	Year	Numbers Available					
33	1954	–	2	3	4	5	6	41	1962	–	2	3	–	5	6
34	1955	1	–	3	4	5	6	42	1963	–	–	3	4	5	6
35	1956	1	2	3	–	–	6	43	1964	–	2	–	–	–	6
36	1957	–	–	–	–	–	6	44	1965	–	2	3	4	5	6
37	1958	1	2	3	4	5	6	45	1966	–	2	–	–	–	6
38	1959	–	2	3	4	–	6	46	1967	–	–	3	–	–	6
39	1960	–	–	3	4	5	6	47	1968	–	–	3	4	5	6
40	1961	–	–	3	4	5	6	48	1969	1	2	3	–	5	–

Available at $4.50 Per Issue

Vol.	Year	Numbers Available						Vol.	Year	Numbers Available					
49	1970	1	–	–	–	5	6	53	1974	–	2	3	4	–	–
50	1971	1	2	3	–	–	–	54	1975	1	2	–	–	–	–
51	1972	–	2	3	–	–	6	55	1976	1	2	3	4		
52	1973	1	2	3	4	–	–								

SINGLE ISSUES PRIOR TO 1954: Write to publisher at address below for listing of issues available at $2.00 each.

BOUND VOLUMES AVAILABLE: $8.00—For Years 1947, 1948, 1949; $10.00—For Years 1953, 1955

OTHER PUBLICATIONS AVAILABLE:

"Basic and Clinical Physiology of the Liver" (Supplement to Sept.-Oct. 1965 issue)—$3.00.

Ten-Year (1960-1969) Cumulative Index—$3.00.

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, Ohio 44122

Please send me the publications circled above, or listed hereunder:

☐ Check for $_____ enclosed.

☐ Please send bill with understanding that ordered material will be sent when payment is received.

Name_____

Address_____

City, State, Zip_____

U.S. Patent applied for.

Ref: Corneal Injuries During General Anesthesia. Anesthesia and Analgesia, Vol. 54, No. 4, July-August, 1975

Protect patients' eyes with

OPTI-GARD™

Why tape eyelids shut and risk skin abrasion, loss of eyelashes, and contact dermatitis? Dupaco Opti-Gard,™ for use during general anesthesia and post-op recovery, effectively and comfortably helps prevent corneal abrasion, lacerations, and scleral hemorrhage. Opti-Gard™ also protects against blood, fluid, or other foreign materials entering the eyes . . . a vital consideration in ENT, head, or neck surgery. Sterile packaged and boxed in convenient dispenser, Opti-Gard™ clear plastic protective covers come with self adhesive foam cushion. **Send for free sample.**

DUPACO
INCORPORATED

P.O. Box 98, San Marcos, Ca. 92069

PRECISE, ECONOMICAL, SAFE . . .

RALS POWER UNIT

. . . INSTANT ATOMIZATION FOR FAST TOPICAL ANESTHESIA

Fast, measured topical anesthesia is ready at your finger tips in a Rals Power Unit. Forget about pumping bulbs, uneven atomization, and limited spraying duration. The Rals Power Unit uses a non-toxic propellant, dichlorodifluoromethane (freon) to activate standard DeVilbiss Atomizers No's. 151, 152 and 163. Instantly, a fine mistlike spray is produced. A graduated solution vial is available for measuring the amount of solution administered.

The Rals Power Unit has been proven effective in cocainization prior to endotracheal intubation, endoscopic instrumentation, laryngotracheal insufflation, and in a variety of nose and throat procedures.

Rals Power Unit #168 are supplied six to a box with adaptor top and metal base. Illustration shows #152 atomizer. All styles in stock.

WRITE OR PHONE FOR LITERATURE, PRICE LIST.

RALS LABORATORIES DIVISION
SCHUEMANN Laboratories, Inc.
480 WEST AURORA ROAD • NORTHFIELD, OHIO 44067

SL-45

In 16 years of use in the United States, FLUOTHANE (halothane) has been administered over 100 million times in a wide variety of surgical procedures. 100 million . . . extensive usage and evaluation that attests to FLUOTHANE as the most widely used inhalant anesthetic.

Since it was first introduced, over 4,000 papers worldwide have been published, ranging from review articles to in-depth studies. 4,000 papers . . . a bibliographic record of note on the most widely used inhalant anesthetic.

In a continuing program of informational services on anesthesiology, Ayerst provides printed and audiovisual aids reflecting the opinions and experiences of recognized authorities in the field. These include the highly regarded series on *Anesthesia Rounds* and *Clinical Aspects of Anesthesiology*, as well as several films of educational value—all available through your Ayerst Representative.

FLUOTHANE® (HALOTHANE) ...OVER 100 MILLION ADMINISTRATIONS

- nonflammable, nonexplosive
- permits use of high concentrations of oxygen
- allows free use of cautery for more adequate control of bleeding
- minimal odor facilitates smooth, rapid induction, reduces patient distress
- early obtundation of pharyngeal and laryngeal reflexes facilitates intubation
- lessens airway problems
- permits rapid adjustment of depth of anesthesia
- emergence is rapid and tranquil with quick recovery of protective reflexes
- minimal nausea and vomiting, shorter recovery room stay

Ayerst®

See last page of advertisement for prescribing information.

FLUOTHANE®

brand of halothane

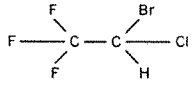
the most widely used inhalant anesthetic

from **Ayerst**

for precision, experience, quality, and service

(Complete text of package circular.)

Description. FLUOTHANE, brand of halothane, is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20° C., and the boiling point (range) is 49° C.-51° C. at 760 mm. Hg. The vapor pressure is 243 mm. Hg at 20° C. The blood/gas coefficient is 2.5 at 37° C., and the olive oil/water coefficient is 220 at 37° C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy: Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

Adverse Reactions. The following adverse reactions have been reported: hepatic necrosis, cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

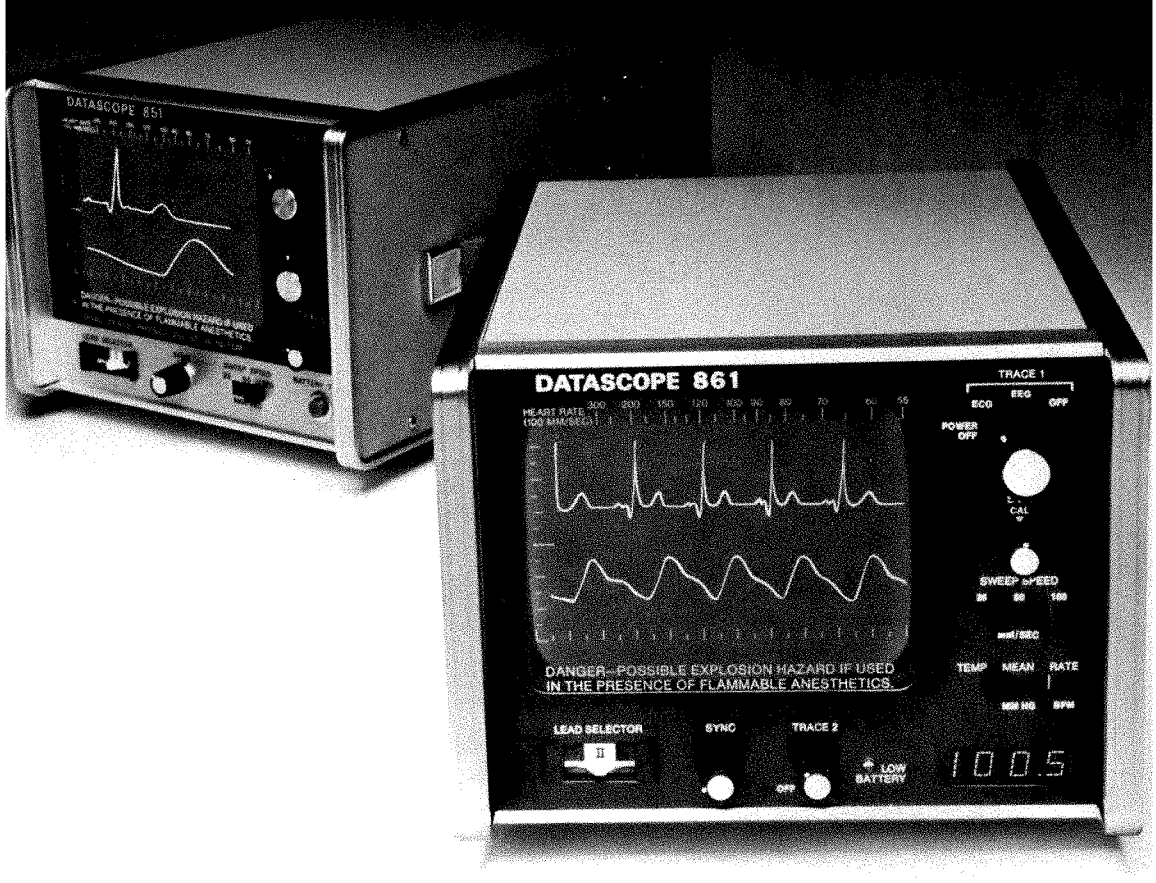
FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

How Supplied. No. 3125—Unit packages of 125 cc. and 250 cc. of halothane stabilized with 0.01% thymol (w/w).

7647

Ayerst AYERST LABORATORIES
New York, N.Y. 10017

THE MOST POPULAR MONITORS MADE. MADE EVEN BETTER.



For some time now, our monitors have been selected for use in surgery by more medical people than any other battery-powered monitors in the world. Because we give you more of what you want in a monitor than any other monitors in the world.

However, this didn't stop us from improving them.

Our new Datascope 851 and 861 will now give you heart rate not only from ECG, but also from pulse or blood pressure.

And both monitors will give you 2 traces. So you can monitor ECG (or EEG) and pulse simultaneously.

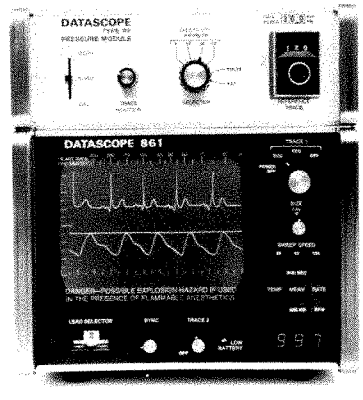
And both give you beat by beat synchronization†. So a single ECG complex shows up with each full sweep.

The 861 does even more. It monitors body temperature. On a digital read-out. And this same digital display will give you heart rate when you want it; or mean blood pressure when you are using the 861 with our Pressure Module.

For all the things our 851 and 861 do, they're surprisingly portable. And they offer longer battery-operating time than any other monitors. In some cases, actually twice as long.

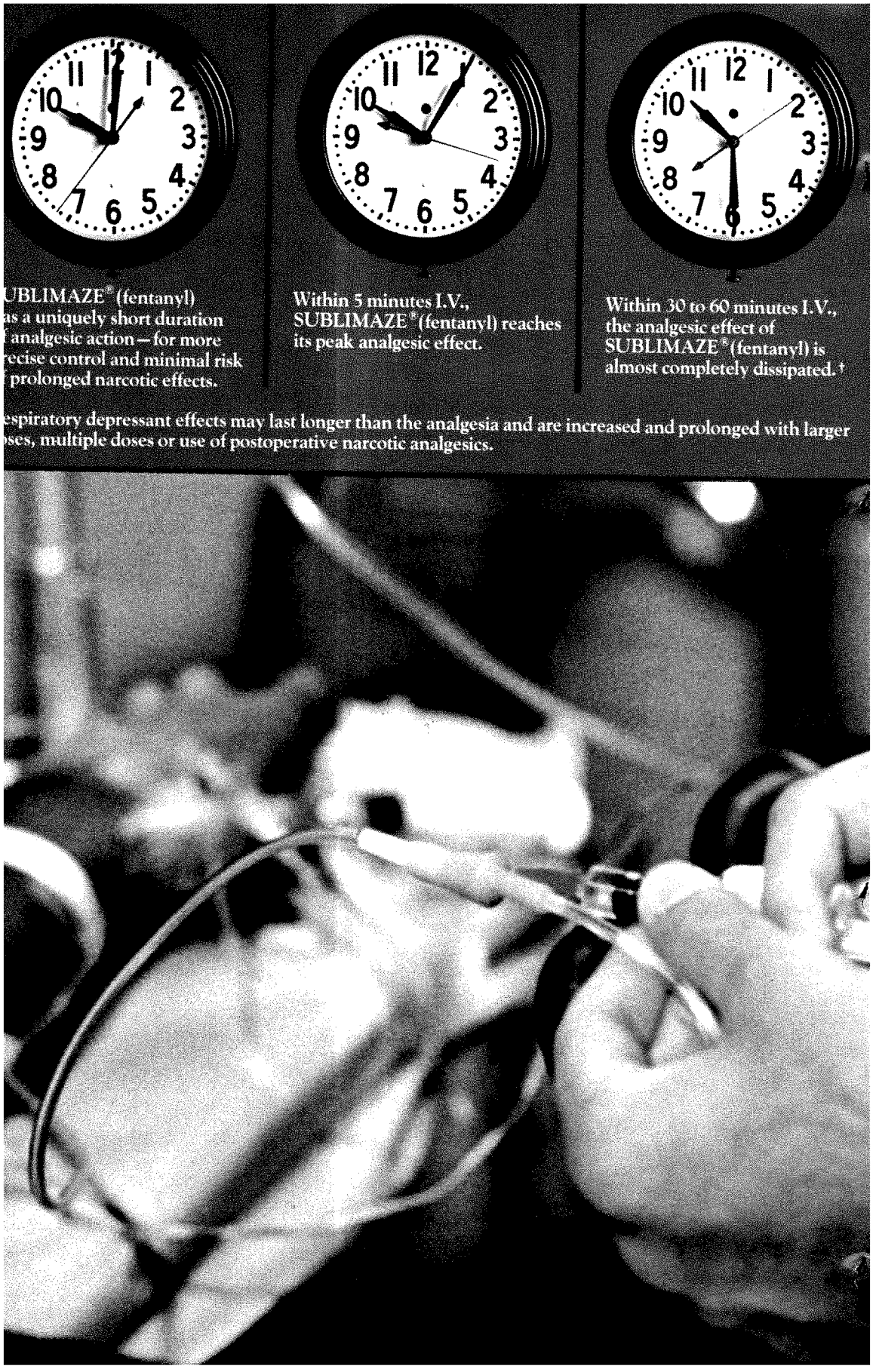
Will they continue to be the most popular monitors made? More so.

For further information about our new 851, 861, or our Pressure Module, write Datascope Corp., 580 Winters Ave., Paramus, NJ 07652.



The 861 with Pressure Module.

THE DATASCOPE 851/861


UBLIMAZE® (fentanyl)
as a uniquely short duration
f analgesic action—for more
recise control and minimal risk
prolonged narcotic effects.
Within 5 minutes I.V.,
SUBLIMAZE® (fentanyl) reaches
its peak analgesic effect.
Within 30 to 60 minutes I.V.,
the analgesic effect of
SUBLIMAZE® (fentanyl) is
almost completely dissipated.†
espiratory depressant effects may last longer than the analgesia and are increased and prolonged with larger
oses, multiple doses or use of postoperative narcotic analgesics.

For potent narcotic analgesic action with rapid onset and short duration:

SUBLIMAZE fentanyl provides profound analgesia without hypnosis and with little or no sedation. With this analgesia as a foundation, it is possible to use light general anesthesia in most cases.

SUBLIMAZE fentanyl is particularly suited for maintenance of analgesia after INNOVAR® injection* has been used for induction. It may also be used preoperatively, during surgery with any common general or regional anesthetic agent, and in the immediate postoperative period whenever the need for potent analgesic action arises.

SUBLIMAZE fentanyl is available both alone and as a component of INNOVAR injection.*

*INNOVAR injection is composed of a 50:1 mixture of droperidol 2.5 mg./cc. and fentanyl 0.05 mg./cc., with lactic acid for adjustment of pH to 3.5 ± 0.3.

SUBLIMAZE® (fentanyl) offers:

☐ Almost immediate analgesia—peak effect within 5 minutes I.V., 8 minutes I.M.

☐ Short duration of analgesic action—30 to 60 minutes with a single I.V. dose of up to 0.1 mg. (Respiratory depressant effects may last longer than the analgesia and are increased and prolonged with larger doses, multiple doses or use of postoperative narcotic analgesics.)

☐ No evidence of liver, heart, or kidney toxicity—expecially valuable in poor-risk patients. However, the drug should be administered cautiously in the presence of liver or kidney dysfunction or cardiac arrhythmias, and the dose should be appropriately reduced in poor-risk patients.

☐ Immediate reversibility by narcotic antagonists.

☐ Little or no histamine release—decreasing the risk of cardiovascular instability.

☐ Minimal emetic effect—has been used successfully to prepare nonfasting patients for awake intubation.

☐ Prevention or reversal of emergence delirium and tachypnea.

SUBLIMAZE® (fentanyl) injection

0.05 mg./cc. as the citrate.
Warning: May be habit forming.
Sodium hydroxide for adjustment of pH to 4.0—7.5

INNOVAR® injection and SUBLIMAZE® (fentanyl) injection are available for use only upon direction of a physician. For information relating to Contraindications, Warnings, Precautions and Adverse Reactions for SUBLIMAZE fentanyl, please turn page.

© McNeil Laboratories, Inc., 1974

SUBLIMAZE® (fentanyl) injection

Description
Each cc. contains:
Fentanyl as the citrate ..... 0.05 mg.
Warning—May be habit forming.
Sodium hydroxide for adjustment of pH to 4.0–7.5

FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY.

Actions SUBLIMAZE fentanyl is a narcotic analgesic with actions qualitatively similar to those of morphine and meperidine. SUBLIMAZE fentanyl in a dose of 0.1 mg. (2.0 cc.) is approximately equivalent in analgesic activity to 10 mg. of morphine or 75 mg. of meperidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. SUBLIMAZE fentanyl appears to have less emetic activity than other narcotic analgesics. Histamine assays and skin wheal testing in man, as well as *in vivo* testing in dogs, indicate that histamine release rarely occurs with SUBLIMAZE fentanyl.

SUBLIMAZE fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. It may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia, and bronchoconstriction.

The onset of action of SUBLIMAZE fentanyl is almost immediate when the drug is given intravenously; however, maximal analgesic and respiratory depressant effect may not be noted for several minutes. The average duration of action of the analgesic effect is 30 to 60 minutes. Following intramuscular administration, the onset of action is from seven to eight minutes, and the duration of action is from one to two hours.

Although the duration of the respiratory depressant effect is unknown, as with other narcotic analgesics it may be considerably longer than the analgesic effect.

Indications SUBLIMAZE fentanyl is indicated:
—for analgesic action of short duration during the anesthetic periods, premedication, induction, and maintenance, and in the immediate postoperative period (recovery room) as the need arises.
—for use as a narcotic analgesic supplement in general or regional anesthesia.
—for administration with a neuroleptic such as INAPSINE® (droperidol) injection as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.

Contraindications SUBLIMAZE fentanyl is contraindicated in patients who are hypersensitive to the drug.

Warnings PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* FENTANYL SHOULD HAVE APPROPRIATE SURVEILLANCE.

RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

If SUBLIMAZE fentanyl is administered with a tranquilizer such as INAPSINE droperidol, the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE fentanyl persists longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as 1/4 to 1/3 those usually recommended. A neuromuscular blocking agent compatible with the patient's condition may be required to control muscle rigidity which may develop with the use of SUBLIMAZE fentanyl.

Drug Dependence: SUBLIMAZE fentanyl can produce drug dependence of the morphine type and therefore has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE fentanyl in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure: SUBLIMAZE fentanyl should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition, SUBLIMAZE fentanyl may obscure the clinical course of patients with head injury.

Usage in Children: The safety of SUBLIMAZE fentanyl in children younger than two years of age has not been established.

Usage in Pregnancy: The safe use of SUBLIMAZE fentanyl has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

Precautions *The initial dose of SUBLIMAZE fentanyl should be appropriately reduced in elderly, debilitated and other poor risk patients. The effect of the initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms (see Actions) SUBLIMAZE fentanyl can also alter respiration. When SUBLIMAZE fentanyl is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia. When used with a tranquilizer such as INAPSINE droperidol, blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE fentanyl should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Postoperatively, respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists (levallorphan, nalorphine, and naloxone; consult individual prescribing information before using). Should respiration be compromised by muscle rigidity, assisted or controlled respiration and possibly a neuromuscular blocking agent will be required. The occurrence of muscle rigidity is related to the speed of intravenous injection and the incidence can be reduced by slow intravenous injection.

When a tranquilizer such as INAPSINE droperidol is used with SUBLIMAZE fentanyl, pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE fentanyl. When patients have received such drugs, the dose of SUBLIMAZE fentanyl required will be less than usual. Likewise, following administration of SUBLIMAZE fentanyl the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE fentanyl should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE fentanyl may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE fentanyl should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE fentanyl is used with a tranquilizer such as INAPSINE droperidol, hypotension can occur. If this occurs the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of INAPSINE droperidol, epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE droperidol.

Adverse Reactions As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE fentanyl are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur.

Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

When a tranquilizer such as INAPSINE droperidol is used with SUBLIMAZE fentanyl, the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with antiparkinson agents. Postoperative drowsiness is also frequently reported following the use of INAPSINE droperidol.

Overdosage ***Manifestations:*** The manifestations of SUBLIMAZE fentanyl overdosage are an extension of its pharmacologic actions.
Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan, or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. Consult the package insert for the individual narcotic antagonists for details about use.

How Supplied SUBLIMAZE® (fentanyl) injection is supplied in 2 cc. (**NDC** 0045-0180-03) and 5 cc. (**NDC** 0045-0180-05) ampuls, in packages of 12.

IMPORTANT: Complete dosage information is available in insert which accompanies each package (or on request). The drug is available only upon direction of a physician.

U.S. Patent No. 3,164,600 9/74

McNEIL McNeil Laboratories, Inc.
Fort Washington, Pa. 19034

MOSBY
TIMES MIRROR

Prepare now for those critical moments. . .

Rely on two new Mosby references for the most current techniques, knowledge, and skills of respiratory therapy and clinical respiratory physiology

A New Book! **RESPIRATORY THERAPY IN CRITICAL CARE.** *By Hugh S. Mathewson, M.D.* This concise volume describes the skills and functions required of respiratory therapists in the critical care situation. Emphasizing the team approach to critical care, the author details team organization and allocation of tasks. Special attention is given to the functions of therapists. The second section of the book discusses the procedures required in many specific critical care situations and covers particular problems in patient management. Diagnostic respiratory function tests are included. September, 1976. Approx. 176 pp., 14 illus. **About $6.95.**

New 3rd Edition! **RESPIRATORY PHYSIOLOGY.** *By N. Balfour Slonim, M.D., Ph.D. and Lyle H. Hamilton, Ph.D.* Now in paperback, this clinically oriented book continues to present basic respiratory physiology in a brief and clear manner. Specialty areas, such as respiratory physiology in lung disease, respiration of the newborn, and respiration in altered environments are thoroughly discussed. New material examines factors affecting oxygen transport by hemoglobin, tests used to detect small airway disease, and mechanically assisted and controlled ventilation. June, 1976. 255 pp., 89 illus. **Price, $9.75.**

MOSBY
TIMES MIRROR

THE C. V. MOSBY COMPANY
11830 WESTLINE INDUSTRIAL DRIVE
ST. LOUIS, MISSOURI 63141

Update an old friend.

With the new universal SLICK™ STYLETTE endotracheal tube guide.

The old familiar way of intubating is not necessarily the better way. The better way to prepare for the unexpected during the critical period of induction and to increase the rate of successful first attempt intubations is to routinely use SLICK STYLETTE. Its non-friction coating eliminates the need for additional lubrication, and the stop-lock controls the extent of its advancement into the endotracheal tube. These features, plus its versatility and malleability reduce the difficulties encountered with normal anatomical variations, such as a small mouth, protruding teeth or bull neck as well as pathological obstacles.

Why not update your procedure with the addition of the SLICK STYLETTE as a standard part of your intubation pack—so it's always there when you need it?

Disposable Slick Stylette is packaged in a sterile Tyvek Mylar peel-away package. Fits all sizes and types of tubes from 3.5mm pediatric to 10.5mm adult.

Reg. U.S. Pat. Off.

Evaluation sample and literature on request.

Medical Products Div. P.O.L.A. Plastics Co., Dept. B
P.O. Box 2086, Van Nuys, Ca. 91408 (213)368-2002

The anesthesia system without compromises is the one you design for yourself. Including Ohio keepables and disposables!

VORTEX® Respiration Monitor measures tidal volumes continuously, totalizes to obtain minute volume.

Disposable Endotracheal Tubes, new, uncuffed or with anatomically designed cuffs for gentle seal. Unique inflation and pilot balloon assembly.

Disposable Anesthesia Breathing Circuit with conductive, cushioned masks in three sizes. Our bacteria filter-pathogen trap fits most anesthesia circuits.

OHIO Critical Care Ventilator with intermittent mandatory ventilation "engineered in." Assists ventilation in any interval from 5 to 100 seconds.

Anesthesia Ventilator, fluidically controlled for less maintenance. Precise and reliable. With a built-in gas evacuator. Ohio can also customize a gas evacuation interface to accommodate your disposal system.

O_2 Monitor with visual and audio alarms.

One system designed to suit all can't really satisfy veryone. Because somewhere along the line you have ɔ compromise. Each of you has your own ideas about ıow best to provide excellence in patient care in your ›wn operating theater. And each OR has its unique ıeeds.

Most new systems begin with one of the four OHIO® ınesthesia machines. Rugged. Practical. Versatile. Functional. Delivering your preference in anesthetic ıgents with accuracy and safety.

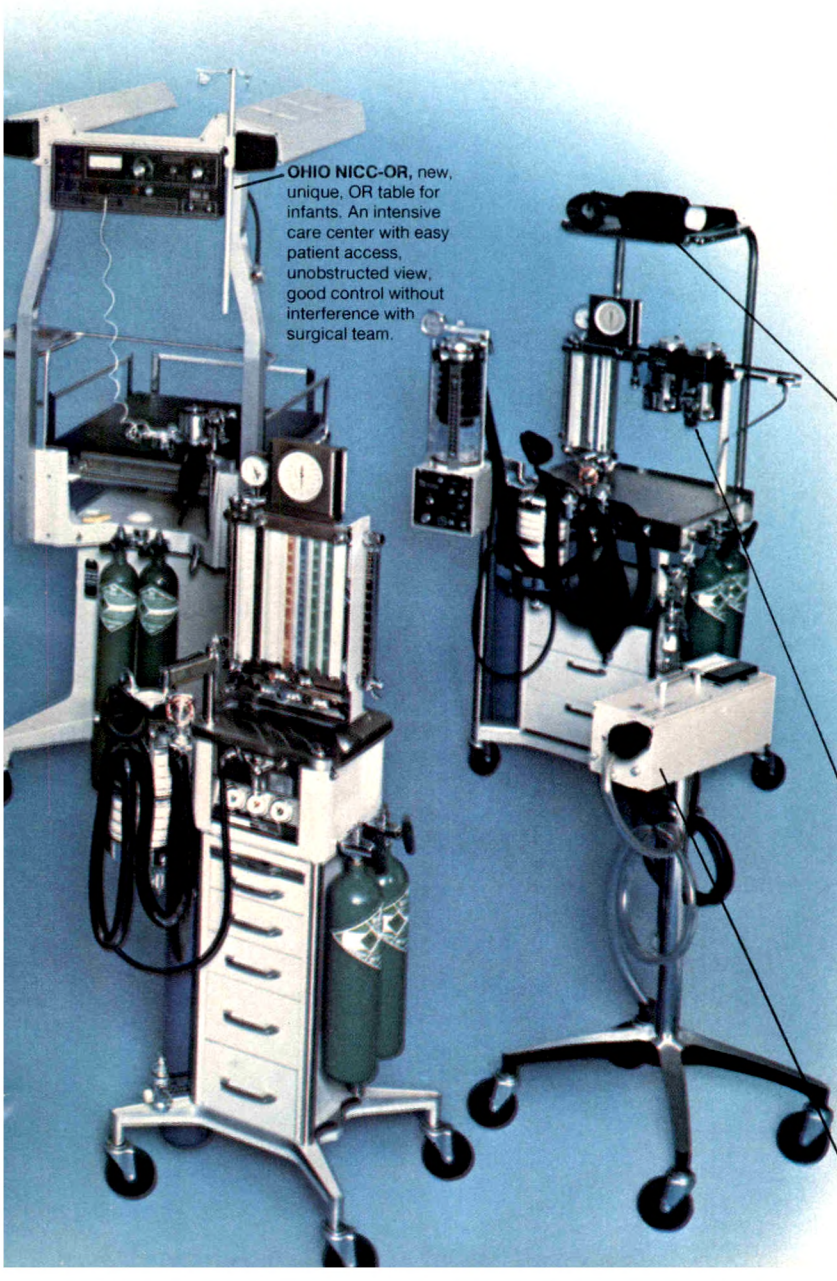
Then, your system grows to support your skills and echniques, as you add accessories and options from Ohio: Vaporizers, ventilators and absorbers, monitors, disposables, medical gases, and gas evacuation ;ystems. And we always have more on the way.

You can depend on over 100 factory-trained Ohio servicemen and six service centers in the U.S. and Canada to keep your anesthesia equipment performing. Plus a knowledgeable sales staff.

Send for information. Or send for your salesman. Ohio will help you develop a reliable, sophisticated anesthesia system. One you can build on when future technologies develop. So, you'll never have to compromise in caring for your patients.

Ohio Medical Products AIRCO®

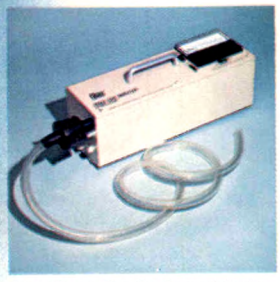
3030 Airco Drive, P.O. Box 7550, Dept. 305
Madison, Wisconsin 53707



OHIO NICC-OR, new, unique, OR table for infants. An intensive care center with easy patient access, unobstructed view, good control without interference with surgical team.

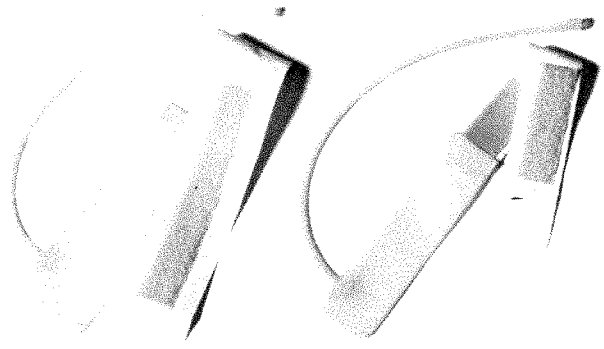
HOPE® II resuscitator with a new valve and the facility to administer enriched oxygen concentrations.

OHIO Calibrated Vaporizer, new, easy-to-use, temperature and flow compensated with excellent low-flow performance.



New Trace Gas Analyzer detects and measures the concentration of nitrous oxide in the operating room atmosphere; alerting OR personnel to leak sources.

The tender touch



These soft, pliable blood pressure cuffs are ideal for use on newborns and infants. Incorporating a Latex bladder, minimizing any chances for skin irritation, and Silicon wrap-around with 12-inch inflating tube. They are secured by the Velcro hook and pile method, with no eyes to hook nor ends to tuck in. They are instantly peeled apart for easy removal.

Cuffs are available in two sizes:
22080 - 1⅜ x 5" (new born)
22081 - 2¼ x 6" (infant)

For additional information write for brochure number 27.

DUPACO
INCORPORATED
P.O. Box 98,
San Marcos, CA 92069

ADDRESS CHANGE NOTICE

International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, Ohio 44122

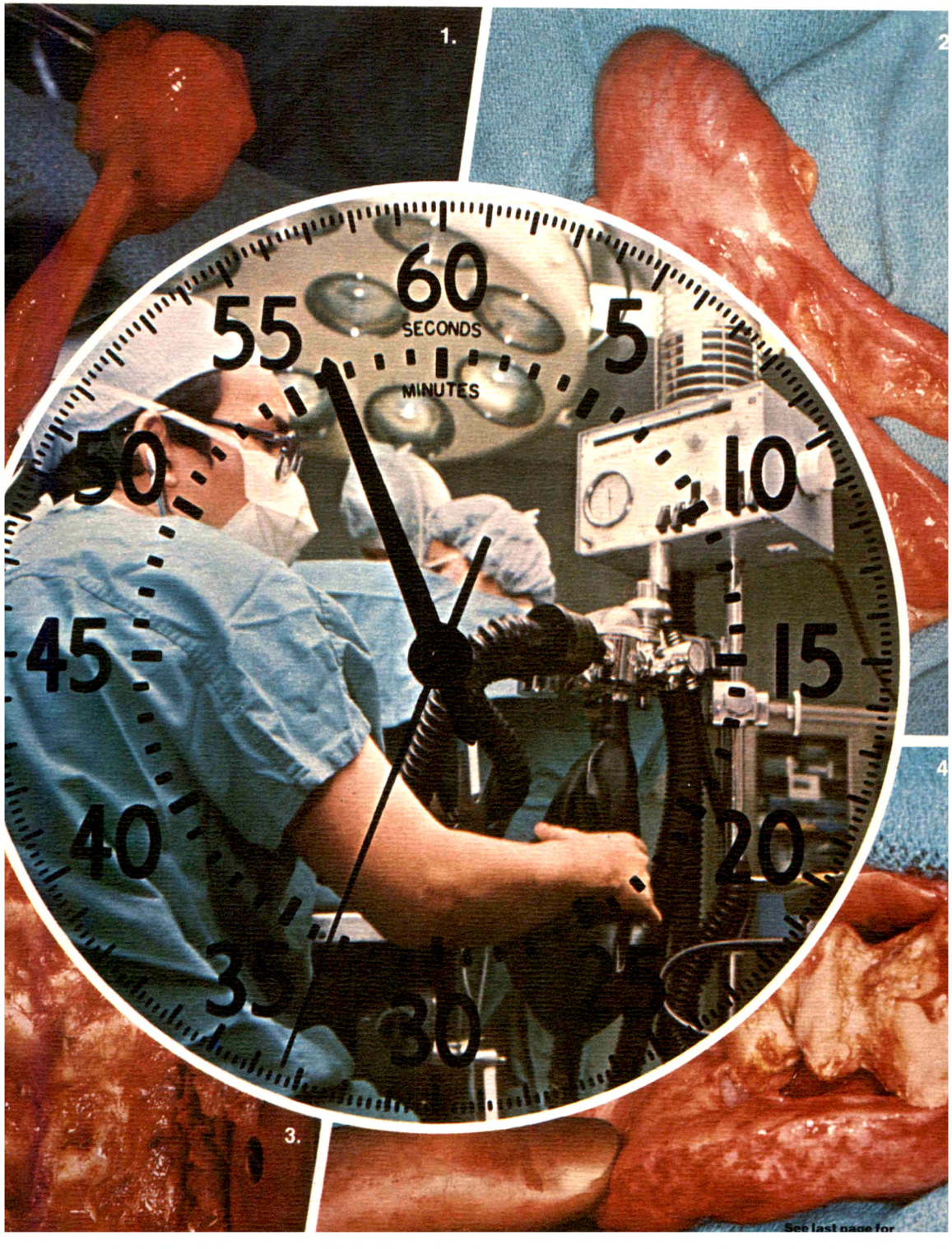
Please change my mail address for ANESTHESIA and ANALGESIA . . . Current Researches, effective _____:

FROM—(Current or former address)	**TO**—(New Address)
Street Address	Street Address
City, State, Zip Code	City, State, Zip Code
Important: Show your name and address exactly as your Journal is now addressed.	Print Your Name

If the Procedure Takes 40 Minutes or More...

You Can Proceed with PAVULON®

pancuronium bromide

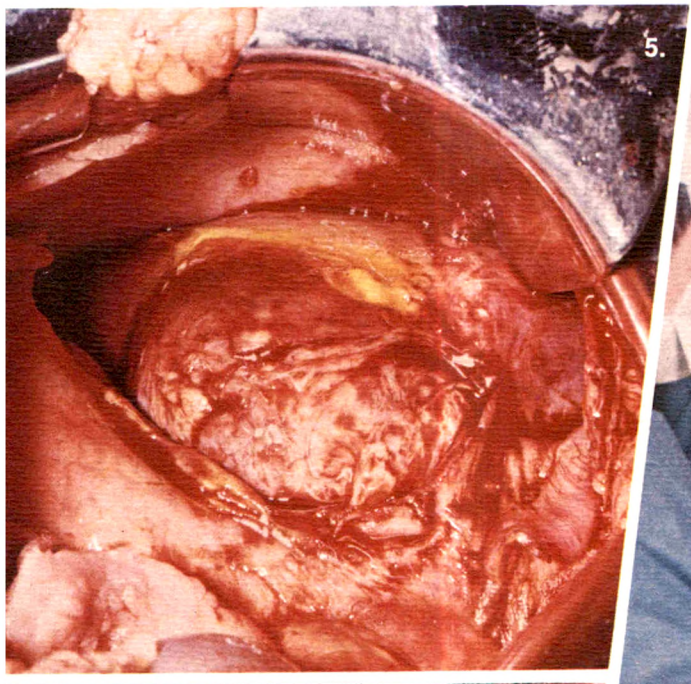


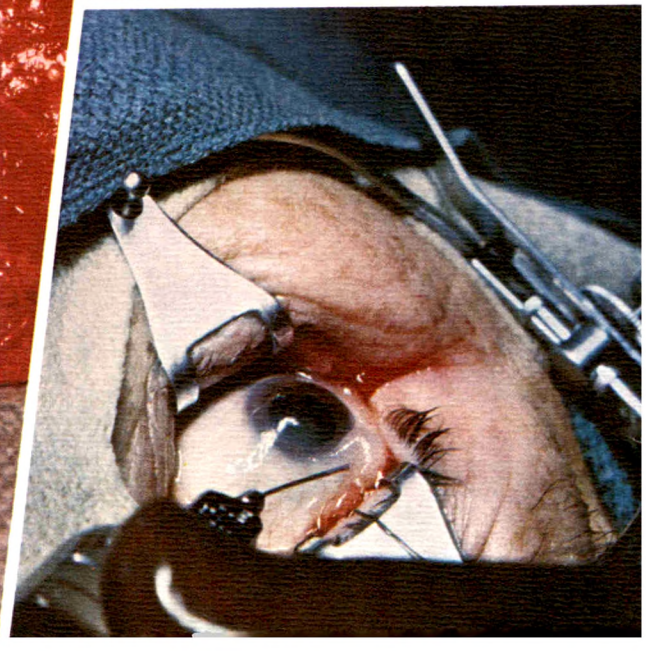
See last page for

Proceed with PAVULON

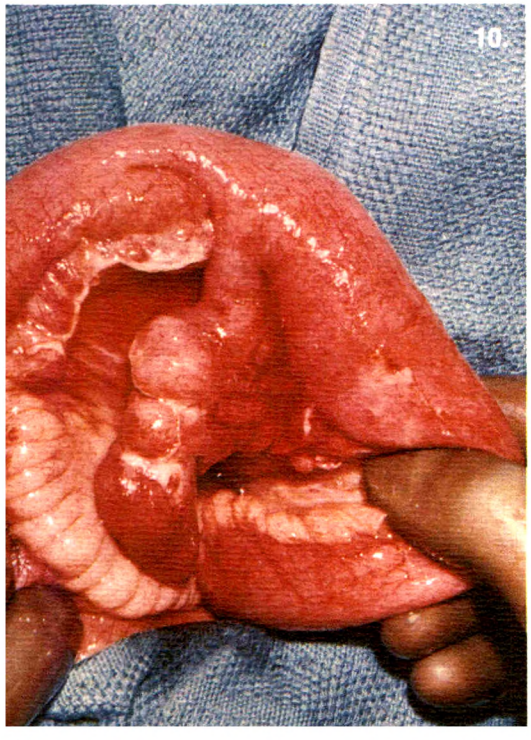
pancuronium bromide

for optimal neuromuscular blockade





No matter where the surgeon's incision



—whatever the part of the body, or the age of the patient, or the cause of surgery, or the system or systems involved —there's a good chance that Pavulon can provide easy, uncomplicated, optimal, neuromuscular blockade.

Initial doses of Pavulon, given to facilitate endotracheal intubation, take effect in approximately 45 seconds and reach their peak at about 2-3 minutes. Once effective blockade is established, it can be maintained with incremental doses of 1 mg or less.

Pavulon is well tolerated, even in the very old, the very young and the very fragile. Histamine release rarely, if ever, occurs; there is little, if any, ganglionic blockade and little effect upon the circulatory system other than an occasional slight rise in pulse rate and blood pressure. There is no muscle pain, no known effects on consciousness, pain threshold or cerebration.

With proper procedure, reversal of Pavulon is relatively simple and generally uneventful. An appropriate antagonist, such as pyridostigmine bromide, can be used. With adequate dosage of the reversal agent, there is relatively little risk of recurarization. In cases of prolonged respiratory depression, other factors (drug interaction, acidosis, hypokalemia, etc.) should be considered.

KEY: ***1.*** *Polypectomy* ***2.*** *Appendectomy* ***3.*** *Spinal fusion* ***4.*** *Nephrolithotomy* ***5.*** *Open heart surgery* ***6.*** *Cesarean section* ***7.*** *Craniotomy* ***8.*** *Aortic-femoral graft* ***9.*** *Cataract removal* ***10.*** *Diverticulectomy (Meckel's)*

Please see last page of advertisement for complete prescribing information.

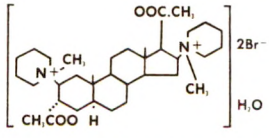
Proceed with PAVULON®

pancuronium bromide

clinically proven nondepolarizing muscle relaxant

THIS DRUG SHOULD ONLY BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: Pavulon (pancuronium bromide) is the aminosteroid 2 beta, 16 beta-dipiperidine-5 alpha-androstane-3 alpha, 17-beta-diol diacetate dimethobromide. It has the following structural formula:



ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon is approximately 5 times as potent as d-tubocurarine chloride.

The onset and duration of action of Pavulon is dose dependent. With the administration of 0.04 mg. per kg. the onset of action, as measured by a peripheral nerve stimulator, is usually within 45 seconds, and its peak effect is usually within 4½ minutes; recovery to 90% of control twitch height usually takes place in less than one hour. Larger doses, more suitable for endotracheal intubation, such as 0.08 mg. per kg. of Pavulon have an onset of action of about 30 seconds, and a peak effect within 3 minutes. Supplemental incremental doses of Pavulon, following the initial dose, slightly increase the magnitude of blockade, and significantly increase the duration of the blockade.

Pavulon has little effect upon the circulatory system. The most frequently reported observation is a slight rise in pulse rate.

Human histamine assays, and clinical observations, as well as in *vivo* guinea pig testing, and in *vitro* mast cell testing, indicate that histamine release rarely, if ever, occurs.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

Pavulon has no known effect on consciousness, the pain threshold, or cerebration.

INDICATIONS: Pavulon is indicated as an adjunct to anesthesia to induce skeletal muscle relaxation. It may also be employed to facilitate the management of patients undergoing mechanical ventilation.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane. No increase in intensity of blockade or duration of action of Pavulon is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. The dosage information which follows has been derived from dose-response studies based on body weight and is intended to serve as a guide only. Since potent inhalational agents or prior administration of succinylcholine enhance the intensity of blockade and duration of Pavulon (see DRUG INTERACTION), these factors should be taken into consideration in selection of initial and incremental dosage.

In adults the initial intravenous dosage range is 0.04 to 0.1 mg. per kg. Later incremental doses starting at 0.01 mg. per kg. may be used. These increments slightly increase the magnitude of the blockade, and significantly increase the duration of blockade, because a significant number of myoneural junctions are still blocked when there is clinical need for more drug.

If Pavulon is used to provide skeletal muscle relaxation for endotracheal intubation, doses of 0.06 to 0.1 mg. per kg. are recommended. Conditions satisfactory for intubation are usually present within 2 to 3 minutes. The ability of the anesthetist to intubate with Pavulon improves with experience.

Dosage in Children: Dose response studies in children indicate that, with the exception of neonates, dosage requirements are the same as for adults. Neonates are especially sensitive to non-depolarizing neuromuscular blocking agents, such as Pavulon, (pancuronium bromide) during the first month of life. It is recommended that a test dose of 0.02 mg. per kg. be given first in this group to measure responsiveness.

Cesarean Section: The dosage to provide relaxation for intubation and operation is the same as for general surgical procedures. The dosage to provide relaxation, following usage of succinylcholine for intubation (see DRUG INTERACTION), is the same as for general surgical procedures.

MANAGEMENT OF PROLONGED NEUROMUSCULAR BLOCKADE: Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Pavulon as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade. Under such circumstances the primary treatment is manual or mechanical ventilation and maintenance of a patent airway until complete recovery of normal respiration is assured. Regonol (pyridostigmine bromide) or neostigmine, in conjunction with atropine, will usually antagonize the skeletal muscle relaxant action of Pavulon. These should be accompanied by or preceded by injection of atropine sulfate to minimize the incidence of cholinergic side effects, notably excessive secretions and bradycardia. Satisfactory reversal can be judged by adequacy of skeletal muscle tone, and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and adjuncts which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade; ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference to the specific package insert of the reversal agents should be made.

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED:

2 ml. ampuls—2 mg./ml.—boxes of 25, NDC #0052-0444-26
5 ml. ampuls—2 mg./ml.—boxes of 25, NDC #0052-0444-25
10 ml. vials —1 mg./ml.—boxes of 25, NDC #0052-0443-25

Organon

Organon Pharmaceuticals
A Division of Organon Inc.
West Orange, N.J. 07052

CLASSIFIED ADVERTISING

CHIEF ANESTHESIOLOGIST for 200-bed hospital—five modern OR's. All surgical services except open heart and neurosurgery. Excellent job challenge. Salary based on past experience and type of appointment. No malpractice insurance required. For information call or write to Dr. Zwemer, Chief Surgeon, Phoenix Indian Medical Center, 4212 North 16th Street, Phoenix, Arizona 85016. (602) 263-1200. The Indian Health Service is a Federal Employer and Federal Civil Service or Public Health Commissioned Corps benefits and requirements apply. Preference is given to qualified Indian or veteran applicants. IHS is an equal opportunity employer.

MARYLAND: Positions on the Anesthesia Staff at Baltimore City Hospitals. Excellent fringe benefits and salary. Residency fully integrated with the Johns Hopkins Medical School program. Send CV to Peter Chodoff, M.D., Anes-in-Chief, Baltimore City Hospitals, 4940 Eastern Ave., Baltimore, Maryland 21224.

PEDIATRIC ANESTHESIOLOGY RESIDENCY

Childrens Hospital of Los Angeles

Three-phase program: Clinical, Academic, Investigative, emphasizing practical aspects of anesthesiology related to infants and children.

AMA approval for third-year residency. Positions available from two months to one year.

Apply: George B. Lewis, Jr., M.D.
Head, Division of Anesthesiology
Childrens Hospital of Los Angeles
4650 Sunset Boulevard
Los Angeles, California 90054
Phone (213) 660-2450, Ext. 2262

PEDIATRIC ANESTHESIA

Newly approved 3rd year Residency. Experience in clinical anesthesia and intensive care medicine according to individual's preference. Openings available July 1977. Contact:

Burton S. Epstein, M.D., Chairman
Dept. of Anesthesiology
Children's Hospital
National Medical Center
2125 - 13th St., N.W.
Washington, D.C. 20009
Tel: (202) 835-4605

APPROVED THIRD YEAR RESIDENCY TRAINING. Designed to develop anesthesiology staff for maternity hospitals. Emphasis on conduction anesthesia techniques. In-depth training, clinical and teaching experience with investigative opportunities and maintenance of general anesthesia skills in gynecology, general surgery and dental surgery. Credited by the University of Pittsburgh. Pennsylvania license required. Positions available for six months or one year.

R. McKenzie, M.D., F.F.A.R.C.S. (Eng.)
Director of Anesthesia
Magee-Womens Hospital
Forbes Avenue and Halket Street
Pittsburgh, PA 15213

ANESTHESIOLOGIST — markedly expanding academic medical center located in attractive Midwestern setting requires additional senior and junior faculty; Board certification and teaching experience necessary; salary from $45,000-$75,000 with extraordinary fringe benefit program. Inquiries with curriculum vitae to Box 5-76-B in care of I.A.R.S.

CHAIRMAN—DEPARTMENT OF ANESTHESIOLOGY

(Board Certified)

938-Bed Medical Complex
University Affiliated—Teaching Hospital
Located in Metropolitan Chicago

Administrative Salary plus Fee for Service Opportunity

APPLY
Director, Professional Services
2520 North Lakeview Avenue
Chicago, Illinois 60614
Attention: Chairman, Search Committee

Rates for classified advertising are $3.00 per line, minimum 5 lines. Box number ads $3.50 per line. Classified Display rates on request. Copy deadline 6 weeks prior to publication. Do not submit payment with order; invoices will be sent for payment prior to publication. Ad copy, subject to acceptance by publisher, should be mailed to: Anesthesia and Analgesia . . . Current Researches, 3645 Warrensville Center Rd., Cleveland, Ohio 44122.

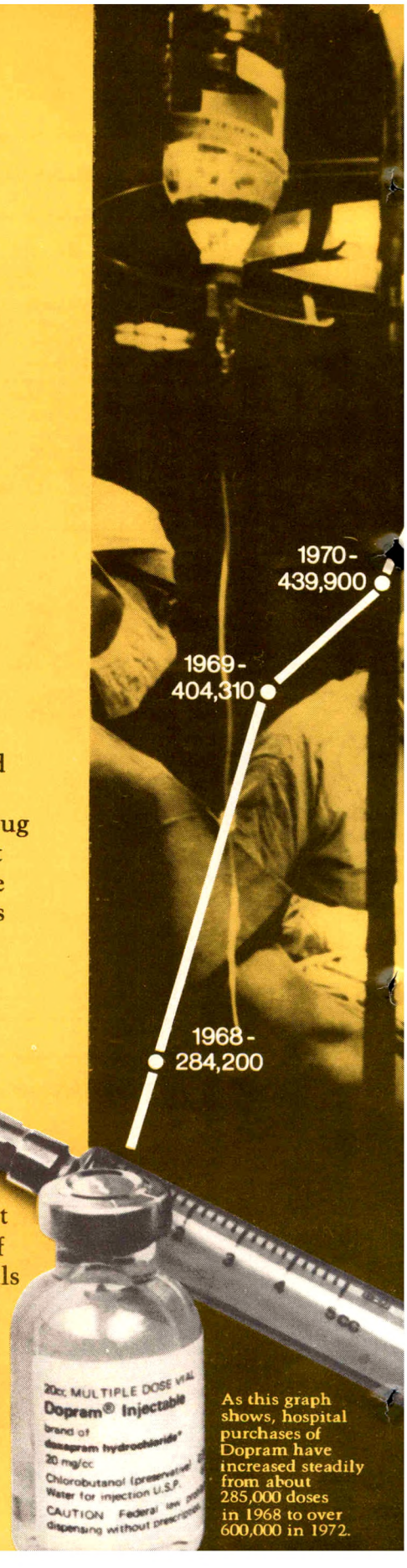
n all types of hospitals
ross the United States,
s usage grows–

Dopram®
njectable
doxapram HCl)

Seven years ago, A. H. Robins introduced Dopram, a unique respiratory stimulant developed in the company's research laboratories. What made this drug so useful to the anesthesiologist was its ability to rapidly restore the respiratory drive in patients with drug-induced post anesthetic depression.

Usage of Dopram has been steadily increasing each year, until today it has become a very important drug in the armamentarium of more than 1,500 hospitals of all types in all 50 states, the District of Columbia, and a number of foreign countries. These hospitals purchased more than 600,000 doses in 1972 alone.

Dopram–an important drug in anesthesiology. Try it for sighs!



As this graph shows, hospital purchases of Dopram have increased steadily from about 285,000 doses in 1968 to over 600,000 in 1972.

...imulate respiration in patients with drug induced post-anesthetic respiratory depression or apnea other than that due to muscle relaxant drugs.
2. To pharmacologically stimulate deep breathing in the so-called "stir-up" regimen in the post-operative patient. Simultaneous administration of oxygen is desirable.
3. To hasten arousal and return of protective pharyngeal and laryngeal reflexes.
4. To aid in the differential diagnosis of post-anesthetic respiratory depression. Failure to adequately stimulate respiration suggests residual muscle relaxant effect.
5. To stimulate respiration, hasten arousal and to encourage the return of laryngopharyngeal reflexes in patients with mild to moderate respiratory and CNS depression due to drug overdosage.

Contraindications—Epilepsy and other convulsive states: incompetence of the ventilatory mechanism due to muscle paresis, flail chest, pneumothorax, airway obstruction, and extreme dyspnea; severe hypertension and cerebrovascular accidents; hypersensitivity.

Doxapram is not recommended for patients 12 years of age or under because studies to evaluate its safety and efficacy have not been performed.

Warnings—Doxapram is an analeptic agent; it is neither an antagonist to muscle relaxant drugs nor a specific narcotic antagonist. Since doxapram has an acid pH, it should not be mixed with alkaline solutions such as thiopental sodium.

Since narcosis may recur after stimulation with doxapram, care should be taken to maintain close observation until the patient has been fully alert for 1/2 to 1 hour. (Duration of drug 5-12 minutes.)

Doxapram is an adjunct to well-accepted supportive measures and resuscitative techniques. It may not stimulate adequate spontaneous breathing or provide sufficient arousal in patients who are severely depressed with CNS depressant drugs.

When doxapram is administered to postoperative patients or to patients in a state of narcosis with chronic pulmonary insufficiency, oxygen should be administered concomitantly. Failure to do so may result in further oxygen debt and more severe dyspnea due to the increased work of breathing.

Doxapram should be administered with great care and only under close supervision to patients with cerebral edema, bronchial asthma, severe tachycardia, cardiac arrhythmia, cardiac disease, hyperthyroidism and pheochromocytoma.

Usage in pregnancy

No adequate clinical studies have been performed to determine the safe use of doxapram in pregnancy. Until further clinical experience has been obtained, the physician must weigh the need against possible risks in using the drug in pregnant patients or in women of child-bearing potential.

Precautions—Recommended dosages of doxapram should be employed and maximum total dosages should not be exceeded. In patients with advanced pulmonary disease with hypoxemia, marked respiratory stimulation increases the work of breathing and may, thus, increase oxygen consumption and carbon dioxide production.

With excessive dosage, hyperventilation induced by doxapram may lead to respiratory alkalosis and hypocapnia with tetany and, theoretically, apnea.

An adequate airway is essential. In order to avoid side effects, it is advisable to use the minimum effective dosage. Monitoring of the blood pressure and deep tendon reflexes is recommended to prevent overdosage.

It is desirable that blood gases (P_{O_2} P_{CO_2} O_2 saturation) be monitored to assess the effectiveness of respiratory stimulation.

Intravenous barbiturates, oxygen and resuscitative equipment should be readily available to manage overdosage manifested by excessive central nervous system stimulation. Slow administration of the drug and careful observation of the patient during administration and for some time subsequently are advisable to insure restoration of the protective reflexes. The possibility of post-[illegible] depression must be kept in mind. In patients who have been lightly curarized, doxapram may temporarily mask the residual effects of muscle relaxant drugs.

Doxapram should be administered cautiously to patients receiving sympathomimetic or monoamine oxidase inhibiting drugs, since a synergistic pressor effect may occur. It should likewise be used with care in post-operative patients with marked dyspnea due to obstructive pulmonary emphysema, acute or chronic asthma, profound metabolic disorders, severe to moderately severe hypertension, increased cerebrospinal fluid pressure, head injury and acute agitation.

Since doxapram may stimulate basal gastric secretion, it should be used with care in patients with peptic ulcer disease and in patients undergoing gastric surgery.

Vascular extravasation or use of a single injection site over an extended period should be avoided since either may lead to thrombophlebitis.

Hypocapnia accompanying forced ventilation is a potent stimulus to cerebral vasoconstriction; it may be postulated that some element of risk may exist from reduced cerebral blood flow following prolonged and intensive hyperventilation.

Since an increase in epinephrine release has been noted with doxapram, it is recommended that initiation of therapy with this respiratory stimulant be delayed for at least 10 minutes following the discontinuance of anesthetics known to sensitize the myocardium to catecholamines, such as halothane and cyclopropane.

As with other intravenous preparations, all precautions should be taken during administration of doxapram to insure that injection is made directly into a suitable vein; extravasation, and inadvertent intra-arterial injection should be avoided.

Adverse reactions—The following adverse reactions have been reported: *Central and Autonomic Nervous Systems.* Hyperactivity feeling of warmth, sweating, muscle tremor, clonus, increased deep tendon reflexes, dizziness, muscle spasticity, pyrexia, confusion, paresthesia, pupillary dilatation, pilomotor erection, headache, bilateral babinski, fasciculation and carpopedal spasm. A grand mal seizure occurred 95 minutes after drug administration in a known epileptic patient who was on anticonvulsant medication.

Respiratory. Cough, dyspnea, laryngospasm bronchospasm and hiccough.

Cardiovascular. Hypertension, sinus tachycardia, bradycardia, extrasystoles, lower T-waves, premature ventricular contractions, irregular heart rhythm, tightness in chest. Although a mild to moderate increase in blood pressure is not infrequent, such an increase may occasionally be of concern in hypertensive patients.

Gastrointestinal. Nausea and/or vomiting, salivation, stimulation of lower bowel, sour taste.

Genitourinary. Urinary retention, stimulation of urinary bladder with spontaneous voiding.

Miscellaneous. Pruritus, thrombophlebitis.

Laboratory Determinations. A decrease in hemoglobin, hematocrit, or red blood cell count has been observed in postoperative patients. In the presence of pre-existing leukopenia, a further decrease in WBC was observed following anesthesia and treatment with doxapram hydrochloride. Elevation of BUN and albuminuria have been observed.

In some of the cases cited above, the patients had received multiple drugs concomitantly, thus preventing an absolute judgment as to the role of doxapram in these reactions.

Dosage—For complete information concerning dosage and administration see package insert.

Supply—Dopram (doxapram hydrochloride) is available in 20 cc rubber-stoppered vials containing 20 mg/cc, with chlorobutanol 0.5% as the preservative.

A. H. Robins Company
Richmond, Virginia 23220

A·H·ROBINS

ANECTINE®
(succinylcholine chloride)
For controlled muscle relaxation adjunctive to anesthesia:

FLO-PACK® for prolonged relaxation

- instant-mix sterile powder interfaces with all major parenteral systems (vacuum or nonvacuum)
- each unit complete—no needle or syringe needed
- retains potency indefinitely
- no refrigeration required
- unbreakable, sterile plastic injection units of 500 and 1,000 mg

INJECTION for short-term relaxation

- a product of choice for intubation and other short procedures
- unique square bottle and bright yellow label for positive identification
- ready for immediate use
- 20 mg per cc . . . in 10 cc multidose vials
- flip-top cap for easy opening
- single or multiple use

ANECTINE®
(succinylcholine chloride)
THE LONG AND SHORT of surgical muscle relaxation

THIS DRUG SHOULD BE USED ONLY BY INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS AND HAZARDS.

DESCRIPTION: Anectine brand Succinylcholine Chloride is an ultra short-acting depolarizing type muscle relaxant. Chemically it is a di-quaternary base consisting of the di-chloride salt of the di-choline ester of succinic acid. It is a white, odorless, slightly bitter powder and very soluble in water. The drug is unstable with alkaline solutions, but relatively stable in acid solutions depending upon the concentration of the solution and the storage temperature. While solutions of succinylcholine chloride are sterilized by autoclaving, they should, nevertheless, be stored under refrigeration to preserve their potency.

INDICATIONS: Succinylcholine chloride is indicated as an adjunct to anesthesia to induce skeletal muscle relaxation. It may be employed to reduce the intensity of muscle contractions of pharmacologically or electrically induced convulsions.

CONTRAINDICATIONS: Succinylcholine is contraindicated for persons with a known hypersensitivity to the drug.

WARNINGS:

WARNING: SUCCINYLCHOLINE SHOULD BE USED ONLY BY THOSE SKILLED IN THE MANAGEMENT OF ARTIFICIAL RESPIRATION AND ONLY WHEN FACILITIES ARE INSTANTLY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND FOR PROVIDING ADEQUATE VENTILATION OF THE PATIENT, INCLUDING THE ADMINISTRATION OF OXYGEN UNDER POSITIVE PRESSURE AND THE ELIMINATION OF CARBON DIOXIDE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR TO CONTROL RESPIRATION.

Succinylcholine should not be mixed with short-acting barbiturates in the same syringe, or administered simultaneously during intravenous infusion through the same needle. Solutions of succinylcholine have an acid pH whereas those of barbiturates are alkaline in reaction. Depending upon the resultant pH of a mixture of solutions of these drugs, either free barbituric acid may be precipitated or succinylcholine hydrolyzed.

Usage in Pregnancy. The safe use of succinylcholine has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

PRECAUTIONS: Low levels of, or abnormal variants of plasma cholinesterase may be associated with prolonged respiratory depression or apnea following the use of succinylcholine. Low levels of plasma cholinesterase may occur in patients with severe liver disease or cirrhosis, severe anemia, malnutrition, severe dehydration, changes in body temperature, exposure to neurotoxic insecticides or those receiving antimalarial drugs. Succinylcholine should be administered with extreme care to such patients and dosage should be minimal. If low plasma cholinesterase activity is suspected, a small test dose of from 5 to 10 mg of succinylcholine may be administered, or relaxation may be produced by the cautious administration of a 0.1% solution of the drug by intravenous drip. Drugs which either inhibit plasma cholinesterase, such as neostigmine or phospholine iodide, or compete with succinylcholine for the enzyme, as does intravenous procaine, should not be given concurrently with succinylcholine.

Succinylcholine should be administered with great caution to patients with severe burns, those recovering from severe trauma, those suffering from electrolyte imbalance, those receiving quinidine, those who have been digitalized recently or who may have digitalis toxicity as serious cardiac arrhythmias or cardiac arrest may result. Great caution should be observed also in patients with pre-existing hyperkalemia or who are paraplegic, have suffered spinal neuraxis injury, or have degenerative or dystrophic neuromuscular disease, or such patients tend to become severely hyperkalemic when succinylcholine is given.

When succinylcholine is given over a prolonged period of time, the characteristic depolarization block of the myoneural junction may change to a non-depolarizing block which results in prolonged respiratory depression or apnea. Under such circumstances, small repeated doses of neostigmine may possibly act as an antagonist. A peripheral nerve stimulator (e.g., the Wellcome Peripheral Nerve Stimulator) may be used to ascertain the type of neuromuscular blockade. If a depolarization block is present both fast (tetanic) and slow (twitch) rates of nerve stimulation are well sustained, and post-tetanic facilitation is absent. If a non-depolarizing block is present there is post-tetanic facilitation and "fade" of successive stimuli on both fast (tetanic) and slow (twitch) rates of nerve stimulation.

Succinylcholine should be used with caution during ocular surgery and in patients with glaucoma. The drug should be employed with caution in patients with fractures or muscle spasm as the muscle fasciculations may cause additional trauma. Muscle fasciculations and hyperkalemia may be reduced by administering a small dose of a non-depolarizing relaxant. If other relaxants are to be used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered.

During the past few years, reports have called attention to a fulminant syndrome, malignant hyperthermia, observed during anesthesia. Its etiology is not fully understood. Malignant hyperthermia occurs in genetically prone individuals of all ages and both sexes receiving potent anesthetics such as halothane, methoxyfluorothane, cyclopropane and diethyl ether. It appears to develop irrespective of the concomitant use of a muscle relaxant, but may be triggered by succinylcholine. Because of the seriousness of this syndrome and the need for early effective treatment of the patient, it is suggested that the continuous monitoring of the temperature will serve as an aid to the early recognition of malignant hyperthermia.

ADVERSE REACTIONS: Adverse reactions consist primarily of an extension of the drug's pharmacological actions. Profound and prolonged muscle relaxation may occur, resulting in respiratory depression to the point of apnea. Hypersensitivity to the drug may exist in rare instances.

The following adverse reactions have been reported: bradycardia, tachycardia, hypertension, hypotension, arrhythmias, cardiac arrest, prolonged respiratory depression or apnea, hyperthermia, increased intraocular pressure, muscle fasciculation, postoperative muscle pain, myoglobinemia and excessive salivation.

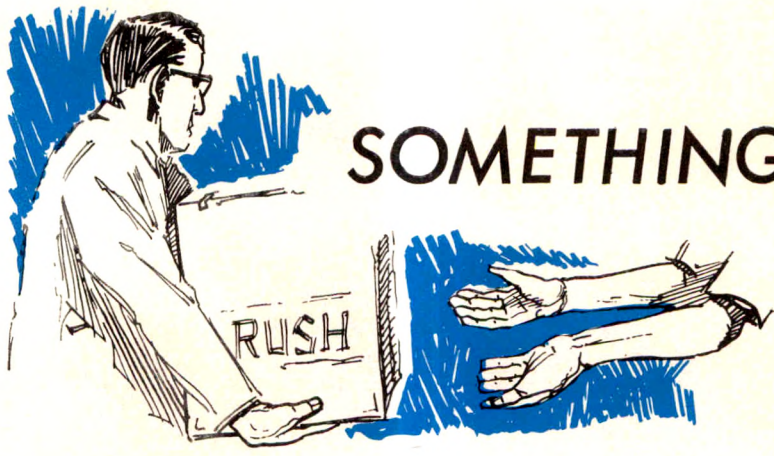
MANAGEMENT OF ADVERSE REACTIONS: Apnea or prolonged muscle paralysis should be treated with controlled respiration.

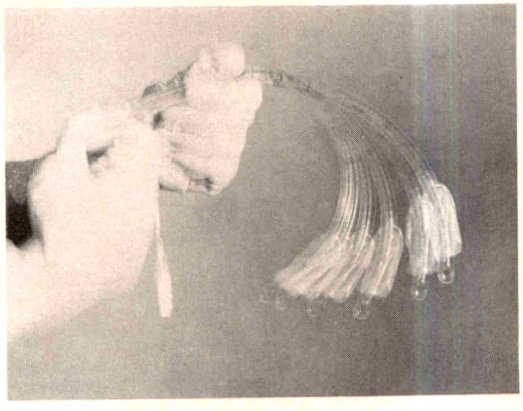
The use of neostigmine to reverse a non-depolarization block is a medical decision which must be made upon the basis of the individual clinical pharmacology and the experience and judgment of the clinician. When neostigmine is used atropine should also be administered.

SUPPLIED: Injection, Multi-dose vials, 20 mg/cc, 10 cc, boxes of 12 vials. Flo-Pack® Sterile Powder 500 mg and 1,000 mg, boxes of 12.

Complete literature available on request from Professional Services Dept. PML.

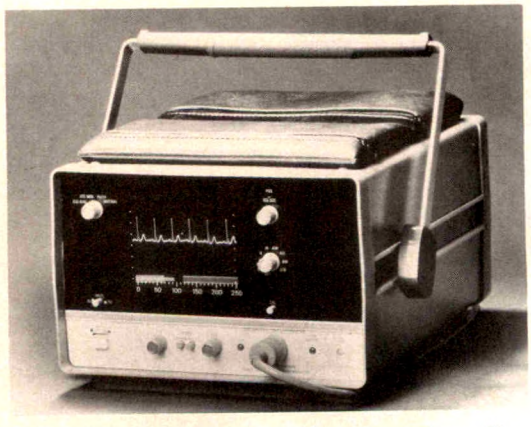
Wellcome
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709





National Catheter Corporation, Argyle, New York, has available the ENDOTROL, an endotracheal tube designed to provide directional tip control for difficult nasal and/or oral intubations. This tube features the hi-lo® cuff to minimize tracheal damage, a Murphy tip and eye with x-ray marker, a pilot balloon and mechanical self-sealing valve. A 15 mm connector is included.

★ ★ ★



Hewlett-Packard, Waltham, Massachusetts, has available two new portable and battery-operated ECG Monitors for operating rooms and monitoring patients in transit, which offer maximum patient and operator protection and minimize display interference from electrosurgery equipment .

The monitors have single-channel, nonfade displays of ECG, pulse or arterial pressure waveforms and bargraph displays of heart rate.

In operating rooms, interference by electrosurgery devices with the monitors' displays are minimized. Special filtering and circuit shielding reject both conducted and radiated energy associated with such radio-frequency (RF) equipment. It is claimed that the likelihood of RF burns at the site of patient electrodes—has been sharply reduced with a special filter in the patient cable.

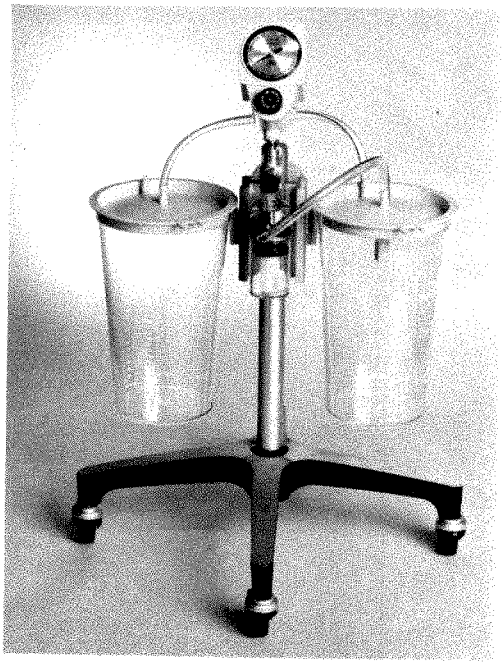
Ohio Medical Products, Madison, Wisconsin, has introduced the OMNI-LAB, a completely automated and self-contained pulmonary function laboratory. The unit tests and computes results to provide accurate and reproducible respiratory diagnostic information.

The integrated Spirometry Module in the OMNI-LAB System has been completely automated to measure and record the patient's Spirogram, Forced Expiratory Vital Capacity (FEVC), Forced Inspiratory Vital Capacity (FIVC) and Maximum Voluntary Ventilation (MVV).

A built-in computer performs all the necessary calculations and calibrations automatically.

An Operator Display provides visual cues to the operator on the appropriate procedures to be followed for each test, and thereby helps insure the proper sequencing of each test. A Patient Display reinforces all operator cues through visual patient instructions. The Patient Display Panel has been incorporated because accurate test results in pulmonary function testing procedures often depend upon the patient's comprehension of precisely what is expected of him.

★ ★ ★



Ohio Medical Products has introduced a Floor Model Suction Bottle Stand for use with the hospital pipeline vacuum systems.

The OHIO Overflow Safety Trap Assembly features a splash deflector to direct incoming fluids to the bottom of the jar, and to act as a seat for the shut-off float for positive overflow protection.

In line with current environmental thinking, Medishield is proud to announce the completion of a totally compatible and comprehensive system which makes pollution-free anaesthesia a reality.

Vital to the concept is the newly-developed Medishield pollution control system. Competitively priced, it features the now well-established anti-pollution valve.

1 Medishield Pollution control system

Precision-engineered to achieve very low resistance to flow, the Medishield anti-pollution system introduces no new anaesthesia technique yet enables waste gases to be safely ducted clear of the theatre. All main components are autoclavable and the system includes a unique feature which gives audible indication of patient respiration.

2 Medishield Manley Servovent

The definitive answer to closed and partial rebreathing circuit techniques. Servo gas consumption is a small fraction of minute volume ventilation while the totally independent servo and patient circuits enable any oil-free available drive gas to be used. The patient circuit can be simply removed in its entirety for sterilization.

A built-in patient safety feature enables spontaneous breathing to take place. The unique fluid logic and patient circuitry give an unprecedented degree of control over tidal volume, inspiratory flow and expiratory time. Any deficiency in gases is automatically compensated by atmospheric air.

3 Medishield Circle Absorber

Utilizing reversible canisters or disposable pre-packs, the Circle Absorber is widely regarded as the finest available. The unique Visidisk system gives at-a-glance confirmation that the valve discs are correctly in place. The absorber is designed for mounting on alternative positions on Boyle tables.

Medishield Boyle International

Now the standard anaesthesia table in many countries of the world, the Boyle International forms a compact, economical foundation for the complete closed-circuit pollution-free anaesthesia station.

Medishield

Manufactured by:

Medishield (Harlow) Limited
Elizabeth Way, Harlow
Essex CM19 5AB, England
Telephone: Harlow (0279) 29692
Cables: Britoxygen Harlow
Telex: 81497

Australia
CIG Medishield

Canada
Medishield Products Ltd

Italy
Saccab SpA

THE COMPLETE POLLUTION-FREE ANAESTHESIA SYSTEM

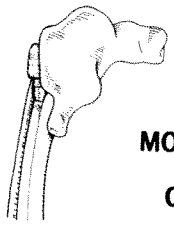
Spain
Material Medico Quirurgico SA (MMQ)

Sweden
Mediada AB

United Kingdom
BOC Medishield

USA
Harris-Lake Inc

The Stripe Symbol and words Medishield, Boyle, Manley and Servovent are BOC Group Trade Marks



FOR MONOSCOPE

MONITORING COMFORT

CUSTOM EARPIECE

Made From Your Own Ear Impression

"Do It Yourself Impression Procedure" Proven At Many Hospitals Over Period of Several Years.

Impression Kit and Full Instructions Complete With Postage Prepaid Mailer $1.00

Lucite Custom Earmold With Coupler . . $8.50

One Week Delivery. Full Guarantee. Full information upon request.

PLASTICAST LABORATORIES, INC.

711 Penn Ave. Pittsburgh, Pa. 15222

Telephone: (412) 281-3357

51ST

CONGRESS

MARCH 6-10, 1977

International Anesthesia Research Society

DIPLOMAT RESORT AND COUNTRY CLUBS
HOLLYWOOD, FLORIDA

Non-conductive blood pressure cuffs . . . in color!

Color-code your departments! Dupaco offers high quality non-conductive blood pressure cuffs in red, blue denim, paisley or plaid. Monogramming available up to 20 stitched letters, with department or individual's name.

Stain resistant, washable, with velcro attaching strips for Dupaco Diasyst.® Sizes listed below. For more information write: Dupaco Inc., P.O. Box 98, San Marcos, CA 92069.

Adult	5¾" x 22"
Medium Adult	5" x 17¾"
Child	3¾" x 14½"
Infant	2¾" x 11½"

DUPACO
INCORPORATED

INDEX OF ADVERTISERS

Air Products and Chemicals, Inc.—*Trace Gas Monitor* (74)
Allergan Pharmaceuticals—*Lacri-Lube*® (14)
American Optical, Medical Division—*Portable Monitors* (11), (12)
Applied Medical Research—*Dinamap Monitor* (33)
Ayerst Laboratories—*Fluothane*® (46), (47), (48)
Datascope Corp.—*Monitors* (49)
Burroughs Wellcome Company—*Anectine*® (64), (65)
Dupaco Incorporated—*Blood Pressure Cuffs* (56)
Dupaco Incorporated—*Non-Conductive Blood Pressure Cuffs* (70)
Dupaco Incorporated—*Opti-Gard*(TM) (45)
J. H. Emerson Company—*IMV Ventilator* (39)
Endo Laboratories—*Narcan*® (6), (7), (8)
Fenwal Laboratories—*Operating Room System* (29), (30), (31), (32)
Harris-Lake, Inc.—*Laryngoscopes* (2)
McNeil Laboratories, Inc.—*Innovar*® (27), (28)
McNeil Laboratories, Inc.—*Sublimaze*® (50), (51), (52)
Medical and Industrial Equipment Div., Claudius Ash, Inc.—*Jackson-Rees T-Piece* (13)
Medishield Corporation Ltd.—*Pollution Control System* (68), (69)
Medsonics, Inc.—*Versatone*® *Doppler* (26)
Merck, Sharp & Dohme—*Aramine*® (21)
C. V. Mosby Company—*Books* (53)
North American Drager—*Narkomed Anesthesia Machine* (25)
Ohio Medical Products—*Anesthesia System* (54), (55)
Ohio Medical Products—*Ethrane*® (18), (19), (20)
O'Neal, Jones & Feldman, Inc.—*Antilirium* (38)
Organon Inc.—*Pavulon*® (57), (58), (59), (60)
Parke, Davis & Co.—*Ketalar*® (34), (35), (36)
Pennwalt Corporation—*Nesacaine*® (16), (17)
Pharmaseal Laboratories—*Anesthesia Trays* (72), (73)
Plasticast Laboratories, Inc.—*Custom Earmold* (70)
P.O.L.A. Plastics—*Slick Stylette* (53)
Professional Instruments Co.—*Peripheral Nerve Stimulator* (37)
A. H. Robins Company—*Dopram*® (62), (63)
Schuemann Labs. (Rals Laboratories Division)—*Rals Power Unit* (45)
Tektronix, Inc.—*Medical Monitor* (15)
Winthrop Laboratories—*Marcaine*® (22), (23), (24)

When to use the word Phär'mə·sēal.

For components, features, "performance" in single-use anesthesia trays, just say the word.

The trays you've counted on from the start now offer you even more to go on.

Back in 1963 we introduced the world's first single-use, regional anesthesia trays.

Today, with a record of safe performance difficult to equal, we offer you an even wider selection of components and features — just as difficult to match — in spinal, caudal and epidural trays.

All with our all-new spinal needle. The needle that's been called the cleanest spinal needle yet. The one with a cannula with almost uncanny smoothness, a cartridge pack with an exceptional point protector, a matched-ground point, metal hub and more.

Trays that offer you a new fenestrated drape with its own adhesive tabs.

A large, moisture-resistant hospital wrap with a new "wrinkle" for better procedure.

Plus, a specially designed introducer needle, a clear 5-cc. Stylex® syringe, a unique aseptic transfer carton...and a variety of other first-quality components and drugs.

But see for yourself what we're talking about. See the trays with performance you can count on. For samples, just call or write.

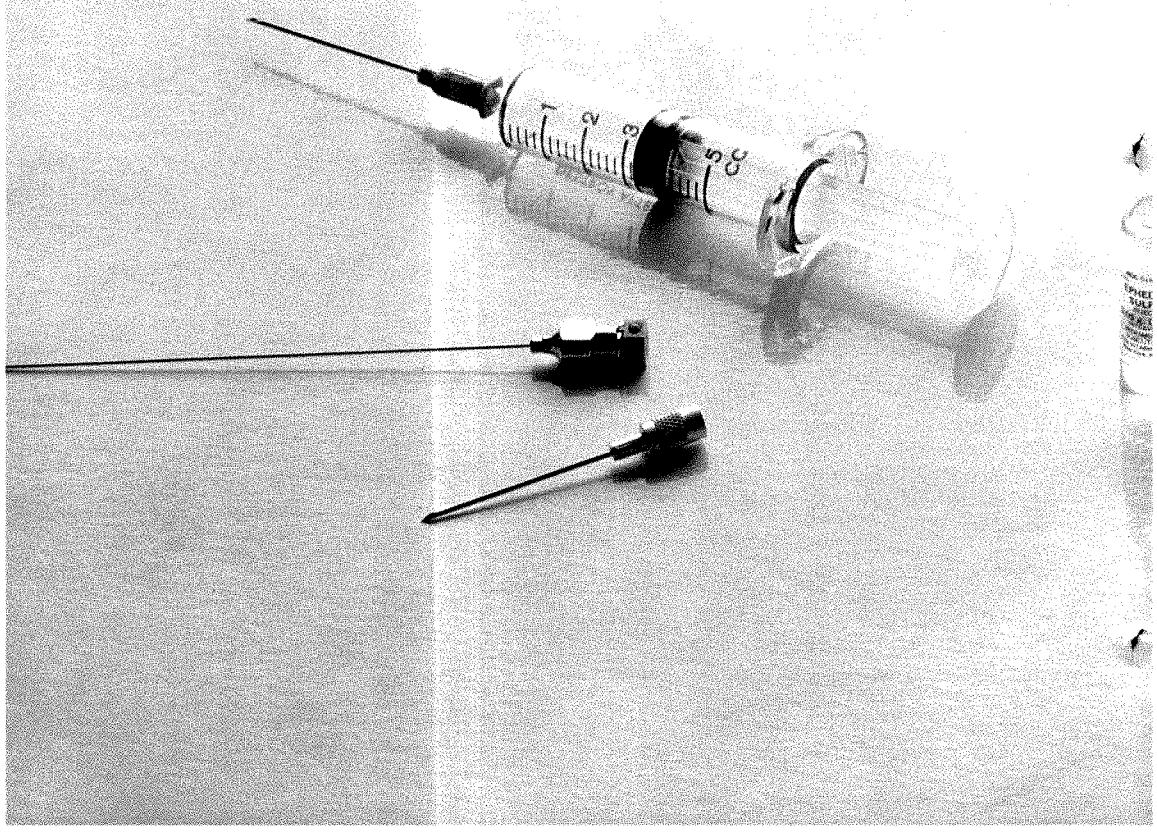
You know the word to use.

IPI®

O.R./ANESTHESIA PRODUCTS BY

PHARMASEAL

GLENDALE, CALIFORNIA 91201



SPINAL ANESTHE
with SPINAL ANES
SPINAL NEEDLE,
LIDOCAINE
HYDROCHLORIDE
Injection, U.S.P.
1% W/V
3 mL
NDC 0143

f You're Confused About O.R. Pollution, Cut It Out.

et a compilation of data on the roblems of trace anesthetic gas nd OR pollution control. Send for ur Positive Response Program.

esides reports and studies to elp you put the problem in erspective, our "PRP" plan of ction provides an up-to-date ook at our products which help ou detect and scavenge trace as in your OR. Key to our pro-ram is the Foregger 410 N_2O race Gas Monitor, a basic equirement for any efficient ace gas monitoring program. 's designed to provide rapid nd continuous sampling of the R air you breathe.

he machine has two sensing odes—Monitor (0-100 ppm) nd Leak Test (0-1,000 ppm). he first mode continuously onitors the ambient air through e gas inlet of the machine. he second permits probing of cal concentrations and sounds repetitive burst alarm as the as concentration increases.

In short, the Foregger 410 N_2O Trace Gas Monitor is a logical first step in solving your OR pollution problem. And there's more. The Scaveng-OR™ Gas Evacuator System, the Protect-OR™ Filter, Wall Suction Systems, and Air-CARE™ Preventive Maintenance Service.

Based on current data, it's likely that routine monitoring of pollution levels and scavenging of waste anesthetic gases will soon be standard Operating Room procedure. We're ready to help you now.

Fill out this ad coupon or ask our Representative for a Foregger PRP Folder. You'll get the problem in perspective and a plan of action to help correct it.

Air Products
FOREGGER

Yes, I am interested in minimizing my O.R. pollution problem. And I want a plan to help correct it. Send me your plan of action.

(Please print or type)

Name Title

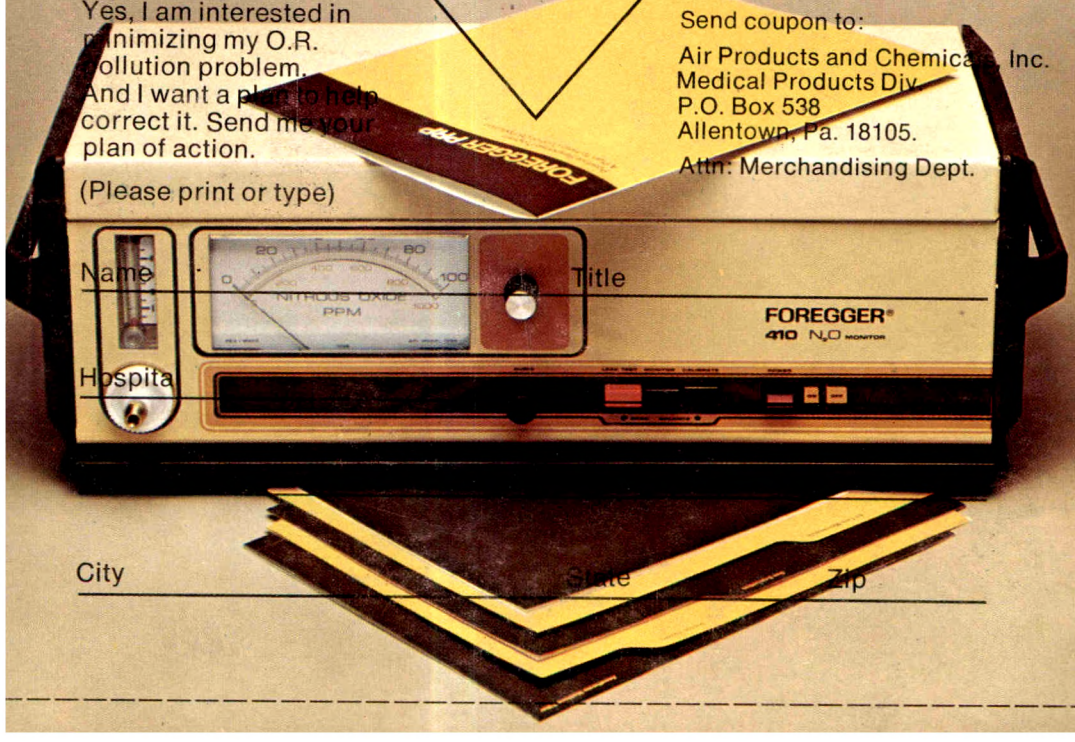
Hospital

City State Zip

Send coupon to:

Air Products and Chemicals, Inc.
Medical Products Div.
P.O. Box 538
Allentown, Pa. 18105.

Attn: Merchandising Dept.



22.3.76

Anesthesia AND Analgesia

.....CURRENT RESEARCHES

The Development of an Acute Tolerance to Ketamine ..... Page 788

Cerebrospinal Fluid Pressure During O_2 Encephalography and N_2O Inhalation ..... Page 849

Annual Index ..... Page 915

Table of Contents ..... Page (4)

Oldest Publication in the Specialty - Established 1922

Journal of the International Anesthesia Research Society

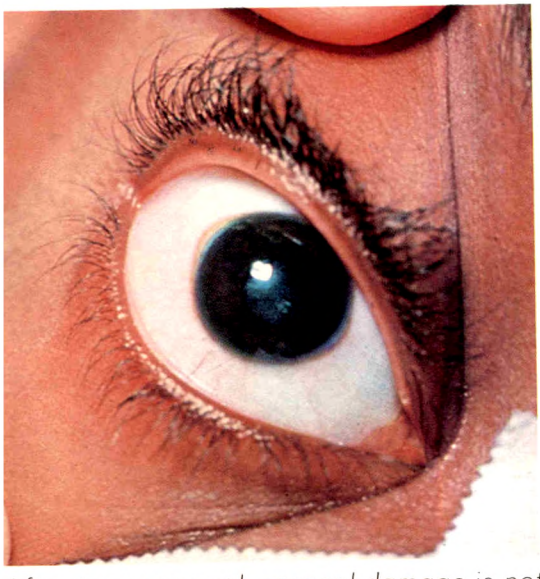
Volume 55, No. 6 November-December, 1976

51st Congress

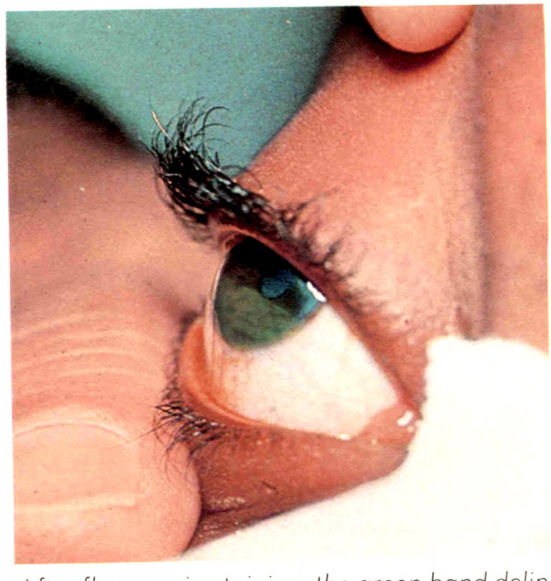
Hollywood, Florida - March 6-10, 1977

LIBRARY

THE UNPROTECTED EYE THAT WAS "PROTECTED" WITH TAPE.



After tape removal, corneal damage is not evident on gross inspection.



After fluorescein staining, the green band delineates area of epithelial injury.

Corneal abrasion...the most common ocular complication of general anesthesia.[1,2] It is painful, may progress to inflammation of the uveal tract, and in the presence of contamination may lead to a serious infection.[1]

This patient's eyes were taped shut and monitored throughout a surgical procedure that lasted several hours. No ocular lubricant was used.[3] The cause of the corneal abrasion is unknown...but it might have been prevented if Lacri-Lube® sterile ophthalmic ointment had been used as an added precaution before the tape was applied.

Lacri-Lube. The first sterile, nonmedicated ophthalmic ointment designed solely to lubricate the eye and protect it against the risk of chemical insult, dehydration, or corneal abrasion.

Whether you tape or not, make Lacri-Lube a part of your standard procedures to minimize the risks of general anesthesia.

LACRI-LUBE®
sterile ophthalmic ointment

IT'S EXTRA INSURANCE.

References: **1.** Snow, J.C. et al: Corneal Injuries During General Anesthesia, Anesthesia and Analgesia 54:465 (Jul-Aug) 1975. **2.** Terry, H.R. et al: Untoward Ophthalmic and Neurologic Events of Anesthesia. Surg Clin N Amer 45:927 1965. **3.** Data on file, Allergan Pharmaceuticals.

ALLERGAN Irvine, California/Pointe Claire, P.Q., Canada

© 1976 Allergan Pharmaceuticals

Anesthesia AND Analgesia ...CURRENT RESEARCHES

JOURNAL OF THE INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

3645 Warrensville Center Road • Cleveland, Ohio, U.S.A. 44122 • Telephones: (216) 295-1124, 295-1130

EDITORIAL BOARD

Editor: T. H. Seldon, M.D., Rochester, Minnesota

Associate Editors:
John T. Martin, M.D., Toledo, Ohio
Emerson A. Moffitt, M.D., Halifax, Nova Scotia
Dean H. Morrow, M.D., Houston, Texas
Edwin S. Munson, M.D., Gainesville, Florida
Robert K. Stoelting, M.D., Indianapolis, Indiana

Contributing Editors:
Douglas B. Craig, M.D., Winnipeg, Manitoba
E. Paul Didier, M.D., Rochester, Minnesota
Ronald W. Dunbar, M.D., Atlanta, Georgia
Leonard C. Jenkins, M.D., Vancouver, British Columbia
David E. Longnecker, M.D., Charlottesville, Virginia
John J. Savarese, M.D., Boston, Massachusetts
N. Ty Smith, M.D., San Diego, California

ANESTHESIA AND ANALGESIA . . . Current Researches is published bimonthly by the International Anesthesia Research Society, a non-profit scientific and educational corporation of the state of Ohio. Members of the Board of Trustees of the Society are: Kenneth K. Keown, M.D., John T. Martin, M.D., Emerson A. Moffitt, M.D., Dean H. Morrow, M.D., Edwin S. Munson, M.D., B. B. Sankey, M.D., T. H. Seldon, M.D., Robert K. Stoelting, M.D. Emeritus Trustees are: Paul R. Dumke, M.D., Morris J. Nicholson, M.D.

EDITORIAL CORRESPONDENCE and manuscripts should be addressed to: **T. H. Seldon, M.D., Editor, Kahler East—Suite C, Rochester, Minnesota 55901, U.S.A. Telephone: (507) 288-8655.** (See "A Guide for Authors" for information concerning manuscript preparation.) Original articles accepted for publication, or papers presented at the Society's annual scientific meetings which are subsequently published in this Journal become the property of the International Anesthesia Research Society, publisher. Reproduction in whole or in part is not permitted except by written consent of the publisher and the author.

BUSINESS CORRESPONDENCE, including subscription and membership payments, single issue purchases, change of address notices, requests for membership applications, should be sent to: **B. B. Sankey, M.D., Executive Secretary and Business Manager, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122. Telephones: (216) 295-1124, 295-1130.**

SUBSCRIPTION RATES: United States and U.S. Possessions: $25.00 per year (6 issues). All Other Countries: $28.00.

MEMBERSHIP DUES (Including Journal Subscription): United States and U.S. Possessions: $25.00 per year; All Other Countries: $28.00. **Membership** available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine or other disciplines who are engaged either in active clinical practice of or research in anesthesiology. **Associate Membership** available to individuals certified, licensed or accredited in anesthesia-related professions (CRNA, ARIT, Physician Assistant). **Educational Membership** (two years for $25.00) available to interns, residents, students in nurse anesthesia and related training programs, upon completion of application including certification by applicant's program director.

SINGLE ISSUES: $4.50 each for years beginning 1970; $3.00 for years 1954-1969; $2.00 for years 1928-1953. (See "Back Issues Available" or write to Cleveland business office for listing.)

REPRINTS: For single copies, write directly to senior author at address listed on title page. Quantity orders (minimum 100) processed through Cleveland business office, prices on request.

MAILING DATES: Journals mailed 25th of January, March, May, July, September and November. Second Class postage paid at Cleveland, Ohio.

CHANGE OF ADDRESS NOTICES: Send to Cleveland business office by first day of the above months to ensure correct addressing of Journals. Replacement copies of missing Journals will be furnished without charge only if original copy is returned by post office as undeliverable.

ADVERTISING: Rate sheets, including advertising clearance procedure, available from national advertising representative: Charles B. Slack, Inc., 6900 Grove Road, Thorofare, New Jersey 08086—Telephone: (609) 848-1000. Orders, contracts, reproduction materials, set copy and classified ad copy should be sent only to Cleveland office.

©1976, International Anesthesia Research Society.

Contents

Volume 55 November-December, 1976 Number 6

SCIENTIFIC ARTICLES

ARTERIAL AND VENOUS PLASMA LEVELS OF BUPIVACAINE FOLLOWING PERIPHERAL NERVE BLOCKS—Moore, Mather, Bridenbaugh, Balfour, Lysons and Horton 763

ADVANTAGES OF INFANT VENTILATORS OVER ADAPTED ADULT VENTILATORS IN PEDIATRICS—Binda, Cook and Fischer 769

KETAMINE AND INTRAOCULAR PRESSURE IN CHILDREN—Ausinsch, Rayburn, Munson and Levy 773

ANESTHESIA AND THE MODIFICATION OF RESPONSE TO INFECTION IN MICE—Duncan, Cullen and Pearsall 776

THE EFFECTS OF STELLATE GANGLION BLOCK ON THE IDIOPATHIC PROLONGATION OF THE Q-T INTERVAL WITH CARDIAC ARRHYTHMIA (THE ROMANO-WARD SYNDROME)—Yanagida, Kemi and Suwa 782

THE DEVELOPMENT OF AN ACUTE TOLERANCE TO KETAMINE—Cumming 788

LORAZEPAM PREMEDICATION: LACK OF RECALL AND RELIEF OF ANXIETY—Fragen and Caldwell 792

ISOENZYMES OF CREATINE PHOSPHOKINASE IN SERUM OF FAMILIES WITH MALIGNANT HYPERPYREXIA—Meltzer, Hassan, Russo and Cho 797

NALOXONE ANTAGONISM AFTER NARCOTIC-SUPPLEMENTED ANESTHESIA—Kripke, Finck, Shah and Snow 800

ENFLURANE AS A PRIMARY ANESTHETIC AGENT FOR PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE—Rodriguez and Gold 806

UNEXPECTED HEPATIC DYSFUNCTION FOUND BY MULTIPLE LABORATORY SCREENING—Schemel 810

POSTPARTUM HYPERTENSION AND CONVULSION AFTER OXYTOCIC DRUGS—Abouleish 813

A SIMPLE TECHNIC TO MINIMIZE TRACHEAL ASPIRATION—Cucchiara 816

THE ANESTHETIC POTENCY OF LIDOCAINE IN THE RAT—DiFazio, Niederlehner and Burney 818

EARLY REVERSAL OF POSTOPERATIVE HYPOXEMIA—Pflug, Lindop, Murphy, Aasheim and Beck 822

LOCAL ANESTHETIC AGENTS—PHARMACOLOGIC BASIS FOR USE IN OBSTETRICS: A REVIEW—Salts, Ott and Walson 829

OBSTETRIC ANESTHESIA TRAINING CENTERS IN THE U.S.A.—1975—Hicks, Levinson and Shnider 839

MEDICAL STATISTICS. STATISTICAL PEARLS III. THE MOST LIKELY INTERPRETATION—Harris 846

CEREBROSPINAL FLUID PRESSURE DURING O_2 ENCEPHALOGRAPHY AND N_2O INHALATION—Paul, Munson and Maniscalco 849

UPTAKE AND EXCRETION OF 1-BROMO-1,2,2-TRIFLUOROCYCLOBUTANE (42M-9) IN MAN: COMPARATIVE STUDY ON PHARMACOKINETICS AND METABOLISM OF INHALATION ANESTHETICS—Holaday and Fiserova-Bergerova 853

CARDIOVASCULAR EFFECTS OF LIDOCAINE DURING ACID-BASE IMBALANCE—Yakaitis, Thomas and Mahaffey 863

CASE HISTORY NUMBER 93: CONGENITAL LOBAR EMPHYSEMA—Martin 869

Anesthesia AND Analgesia . . . Current Researches

SCIENTIFIC ARTICLES—November-December, 1976 (Continued)

BRIEF REPORTS

BRONCHIAL BLOCKADE IN A CHILD WITH A BRONCHOPLEURAL-CUTANEOUS FISTULA USING A BALLOON-TIPPED CATHETER—Cant, Tinker and Tarhan 874
DIFFICULT EXTUBATION OF AN ENDOTRACHEAL TUBE CUFF—Ng and Datta 876
HUMIDITY OUTPUT OF THE COLUMBIA PEDIATRIC CIRCLE—Ramanathan, Chalon, Rand and Turndorf 877
MODIFICATION OF A BIRD® MARK-14 ANESTHESIA VENTILATOR FOR GREATER VERSATILITY—Jones 879
DECREASED ARTERIAL OXYGENATION DURING SODIUM NITROPRUSSIDE ADMINISTRATION FOR INTRAOPERATIVE HYPERTENSION—Seltzer, Doto and Jacoby ... 880
AN ANESTHETIC GAS SCAVENGER FOR THE JACKSON-REES SYSTEM—Cestone, Ryan and Loving 881
A METHOD FOR INSERTING THE CARDEN TUBE—Cooke, Hood and Thomas 882
COMPARISON OF DOT TEST AND DIGIT-SYMBOL TEST FOR STREET FITNESS OF OUTPATIENTS— Ritter and Anderson 883
ACUTE MAXILLARY SINUSITIS COMPLICATING NASOTRACHEAL INTUBATION: A CASE REPORT—Gallagher and Civetta 885
SUPINE HYPOTENSIVE SYNDROME CAUSED BY INTRA-ABDOMINAL MASS: A CASE REPORT—Kim, Buakham and McAmis 887

FEATURES

People and Places ..... (13)
Correction: Estimation of Anesthetic Solubility in Blood—Feingold 838
Becton, Dickinson and Company Lecturer for 51st Congress—William K. Hamilton, M.D. 890
Baxter-Travenol Lecturer for 51st Congress—Arthur C. Guyton, M.D. 891
We Salute—Richard George Barton Gilbert, F.R.C.P. (C) . 892
Correspondence:
Method to Identify a Cervical Esophageal Diverticulum During General Anesthesia—Nicholson and McAlpine .. 893
Accuracy, Brevity, Clarity: Three Principles of Good Medical Writing—Shephard 893
Write to Inform, Not to Impress—Eibel .. 895
Use of Monitor for Ketamine in Radiotherapy—Feingold 895
What Route of Administration for K^+ Solutions?—Fanning 895
How Do Benefits of Hemodilution Balance O_2 Reduction?—Kopman 897
Effect of $Paco_2$ on O_2 Consumption During Cardiopulmonary Bypass—Kopman 898
Editor's Choice 900
The Physician and The Law 906
Questions and Answers 907
Acknowledgment to Guest Reviewers 909
Books Received 911
Annual Index 915
Title Page for Binding, Volume 55 939
Scientific Articles, Next Issue ..... (37)
A Guide for Authors ..... (38)
Back Issues ..... (40)
Classified Advertising ..... (59)
Something New ..... (53)
Index of Advertisers ..... (69)

In 16 years of use in the United States, FLUOTHANE (halothane) has been administered over 100 million times in a wide variety of surgical procedures. 100 million ...extensive usage and evaluation that attests to FLUOTHANE as the most widely used inhalant anesthetic.

Since it was first introduced, over 4,000 papers worldwide have been published, ranging from review articles to in-depth studies. 4,000 papers... a bibliographic record of note on the most widely used inhalant anesthetic.

In a continuing program of informational services on anesthesiology, Ayerst provides printed and audiovisual aids reflecting the opinions and experiences of recognized authorities in the field. These include the highly regarded series on *Anesthesia Rounds* and *Clinical Aspects of Anesthesiology*, as well as several films of educational value—all available through your Ayerst Representative.

FLUOTHANE® (HALOTHANE) ...OVER 100 MILLION ADMINISTRATIONS

- nonflammable, nonexplosive
- permits use of high concentrations of oxygen
- allows free use of cautery for more adequate control of bleeding
- minimal odor facilitates smooth, rapid induction, reduces patient distress
- early obtundation of pharyngeal and laryngeal reflexes facilitates intubation
- lessens airway problems
- permits rapid adjustment of depth of anesthesia
- emergence is rapid and tranquil with quick recovery of protective reflexes
- minimal nausea and vomiting, shorter recovery room stay

Ayerst

See last page of advertisement for prescribing information.

FLUOTHANE®

brand of halothane

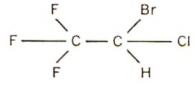
the most widely used inhalant anesthetic

from Ayerst

for precision, experience, quality, and service

(Complete text of package circular.)

Description. FLUOTHANE, brand of halothane, is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20° C., and the boiling point (range) is 49° C.-51° C. at 760 mm. Hg. The vapor pressure is 243 mm. Hg at 20° C. The blood/gas coefficient is 2.5 at 37° C., and the olive oil/water coefficient is 220 at 37° C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy: Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

Adverse Reactions. The following adverse reactions have been reported: hepatic necrosis, cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

How Supplied. No. 3125—Unit packages of 125 cc. and 250 cc. of halothane stabilized with 0.01% thymol (w/w).

7647

Ayerst **AYERST LABORATORIES**
New York, N.Y. 10017

It works like a magnet; not just a strainer.

lew electrostatic filter element ttracts, traps and holds over 99% f the pathogens found in the nesthesia system. Not just acteria, but viruses as well, *egardless of size.* Tests* prove hat the patented Nicholes "99" is he most practical and effective lter available, affording pro- ection against both infections nd malpractice suits. It is light- veight and multi-directional, and hay be interposed in different ositions within the anesthesia ystem. Its unique filter trap with inimal air resistance eases atient breathing even under ad- erse respiratory conditions or igh relative humidity.

The Complete Circuit.
The finest conductive, disposable anesthesia circuit, it is manufactured to the highest medical standards, at low, competitive prices.

The complete circuit includes two flexible, lightweight breathing tubes, a 3-litre breathing bag and a specially-engineered swivel wye piece for maximum compactness and mobility. Plus the amazingly efficient disposable Nicholes 99 Bacterial and Viral Retentive Filter. Filters and individual components may be ordered separately. Available from your surgical or hospital supply dealer, or call K&G for name of nearest supplier. Dealer inquiries invited. Mail the coupon now.

K&G

Research findings available upon request.

K&G Healthcare Industries, Inc.
P.O. Drawer #168, Goldsboro, N.C. 27530
(919) 731-2283

- ☐ Please send me further information on the Nicholes "99" Filter.
- ☐ Please arrange a demonstration for me on the Nicholes "99" Filter.

Name _____ Title_____

Institution Name _____

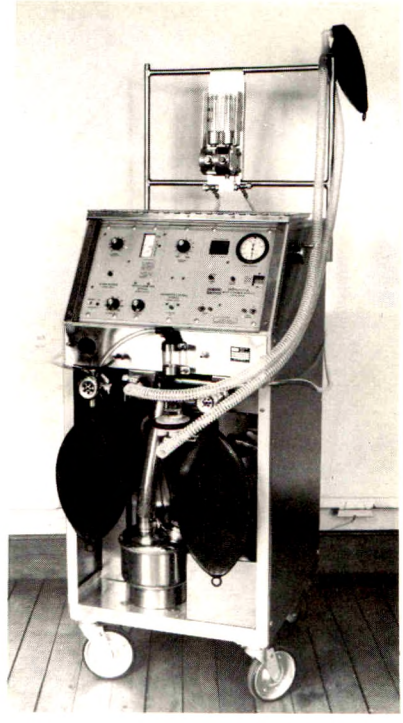
Address _____

City _____

State _____ Zip_____

EMERSON IMV *Ventilator*

Intermittent Mandatory Ventilation



Continuous-flow voluntary ventilation, with intermittent forced breaths, is an alternative to assisted or controlled respiration. It has been found especially valuable for infants and for use in "weaning" adults as they improve.

Air fully humidified (and usually enriched with oxygen) flows continuously to a reservoir bag, and is available for unobstructed inspiration by the patient. A slight expiratory back-pressure (PEEP) may be added, to keep the lungs expanded. At intervals the ventilator delivers a "mandatory" breath, which supplements the patient's own breathing activity and increases minute volume. The machine does not have to "take over". The patient maintains his own homeostasis, without interference from drugs or hyperventilation.[1]

At first the ventilator is generally set to supply mandatory breaths at a normal controlled rate. This controlled respiration is then gradually changed, by lengthening the interval between breaths (a second or two at a time) as the patient's condition improves. Eventually mandatory breaths are spaced so far apart that the patient scarcely relies on them at all — and "weaning" is completed.[2]

VERSUS ASSIST

Triggering an assistor has often been a problem, particularly for infants, since their rates are rapid and their inspiratory impulses are slight. If synchronization is less than perfect, the patient inhales (at least part of the time) with no fresh gas available. Under such circumstances, blood levels of CO_2 rise, as noted by Kirby and associates.[1]

VERSUS CONTROL

For apneic patients, control is obviously needed. But to take over, when a patient is breathing spontaneously, drugs have to be used or the patient has to be hyperventilated. Either procedure has drawbacks. Paralytic or sedative agents may obscure signs of neurological or metabloic disorders. Lowered muscle tone may impair venous return, and hence cardiac output. The effects of such drugs are particularly hard to predict in infants.

Hyperventilation (often used to suppress spontaneous breathing efforts) has drawbacks, too. The resultant alkalosis reduces cerebral blood flow. Blood levels of calcium and magnesium are altered. Airway resistance increases and pulmonary compliance decreases with hypocarbia.[3] Finally, there is evidence of a shift in the carbon dioxide response curve, which makes weaning more difficult.

All of these pit-falls can be avoided by using continuous-flow IMV.

Please request Form 3-MV.

J. H. EMERSON COMPANY

CAMBRIDGE, MASSACHUSETTS 02140

CALIBRATION ...is a must

NEW! tec-care™ SERVICE AGREEMENT

Cleaning of FLUOTEC and other TEC type vaporizers is frequently confused with *calibration* of these units.

Proper calibration to factory specifications, essential for safe operation, can only be accomplished by using a complex optical system — The Refractometer.

Vaporizers should be calibrated with a Refractometer *at least* once a year.

HARRIS-LAKE now offers a new preventive maintenance contract (TEC-CARE™), a low-cost service contract that will assure factory service at the *proper* time to the *proper* vaporizer with the *proper* equipment— with *guaranteed* calibration/verification.

Additional Details on Opposite Side

HARRIS-LAKE, INC.
5600 SOUTH MARGINAL ROAD
CLEVELAND, OHIO 44103
WATS LINE 800/321-7100

FOR COMPLETE FORMATION, FILL OUT

THIS CARD

Please send complete TEC-CARE™ Service Agreement to:

Name_____

Hospital_____

Address_____

City, State, Zip_____

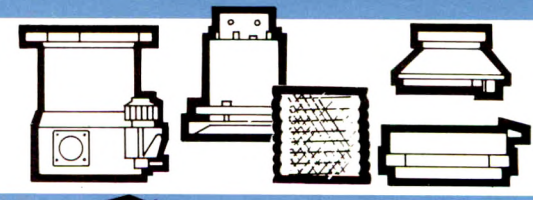
Department_____

HARRIS-LAKE INTRODUCES...

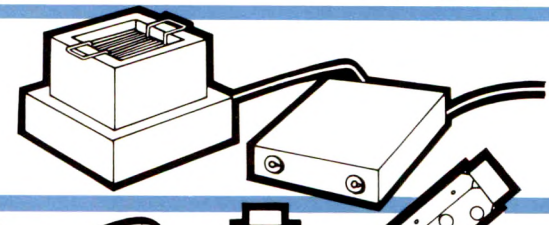
tec-care™

A PROGRAM THAT ASSURES YOU OF A REGULAR, GUARANTEED SERVICING OF YOUR VAPORIZER BY:

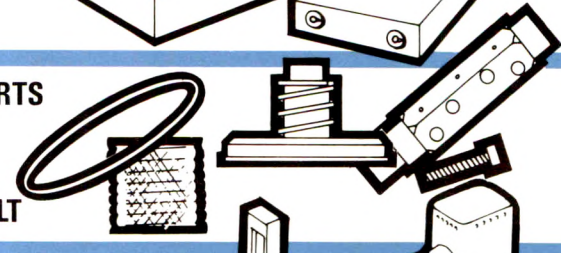
1 COMPLETE DISMANTLING OF THE INSTRUMENT AND PARTS CHECK FOR DAMAGE AND WEAR



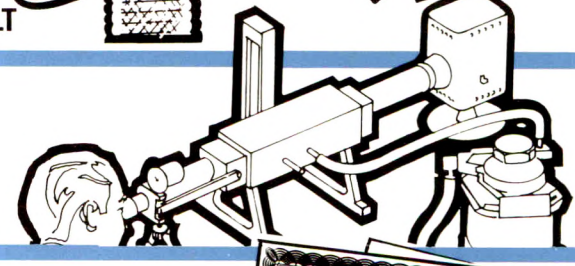
2 CLEANED IN AN ULTRASONIC BATH



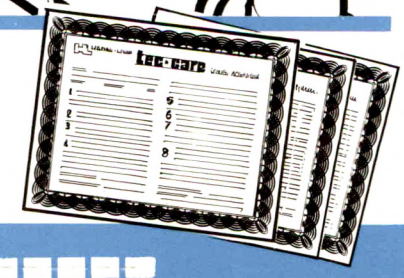
3 WICKS AND SMALL PARTS ARE REPLACED AT NO CHARGE AND THE INSTRUMENT IS REBUILT



4 OVER TWENTY CALIBRATION CHECKS ARE MADE



5 GUARANTEED ACCURACY TO MANUFACTURER'S SPECIFICATION



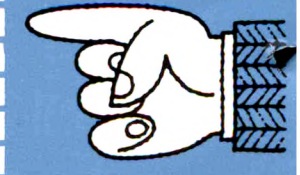
FIRST CLASS PERMIT
No. 21391
CLEVELAND
OHIO

BUSINESS REPLY MAIL
postage stamp necessary if mailed in the United States

— POSTAGE WILL BE PAID BY —

HARRIS-LAKE, INC.
5600 South Marginal Road
Cleveland, Ohio 44103

FOR COMPLETE INFORMATION, FILL OUT



THIS CARD

PEOPLE and PLACES

Intensive Care sponsored by the Department of Anesthesiology University of Miami School of Medicine will be presented on a Caribbean Cruise aboard S/S Doric, January 6-15, 1977. Contact: **Sonja Auxier,** Department of Anesthesiology, University of Miami School of Medicine, P.O. Box 540875, Biscayne Annex, Miami, Florida 33152.

★ ★

The Second International Symposium on Malignant Hyperthermia, sponsored by the Department of Anesthesiology and the University of Colorado School of Medicine will be held at the University of Colorado Medical Center on April 1, 2, 3, 1977. For further information write: **J. Antonio Aldrete, M.D.,** University of Colorado Medical Center, Box B113, Denver, Colorado 80262.

★ ★

Annual Meeting, Society for Obstetric Anesthesia and Perinatology. Edgewater Inn, Seattle, Washington, will be held April 14-17, 1977.

For more information, write: **David Ralston, M.D.,** Department of Anesthesia, University of Washington, School of Medicine, Seattle, Washington 98105.

★ ★

The Department of Anesthesia, Boston Hospital for Women and Harvard Medical School, Boston, Massachusetts, will present a course entitled "Obstetric Analgesia and Anesthesia," May 6-7, 1977.

This course is designed to present a review and update on obstetric anesthetic management.

Course directors: **Gerard W. Ostheimer, M.D.,** and **Milton H. Alper, M.D.**

For more information write: Department of Continuing Education, Harvard Medical School, 25 Shattuck Street, Boston, Massachusetts 02115.

★ ★

The First Colorado Anesthesiology Symposium sponsored by the Colorado Society of Anesthesiologists and the Office of Postgraduate Education and the Department of Anesthesiology of the University of Colorado School of Medicine will be held at the Broadmoor Hotel in Colorado Springs on July 30-31, 1977. The seminar will deal with anesthesiology and the cardiac patient. Further details may be obtained from **Dr. J. Antonio Aldrete,** University of Colorado Medical Center, Box B113, Denver, Colorado 80262.

The best anesthesia system without compromises is the one you design for yourself. Including Ohio keepables and disposables!

VORTEX™ Respiration Monitor measures tidal volumes continuously, totalizes to obtain minute volume.

Disposable Endotracheal Tubes, new, uncuffed or with anatomically designed cuffs for gentle seal. Unique inflation and pilot balloon assembly.

Disposable Anesthesia Breathing Circuit with conductive, cushioned masks in three sizes. Our bacteria filter-pathogen trap fits most anesthesia circuits.

OHIO Critical Care Ventilator with intermittent mandatory ventilation "engineered in." Assists ventilation in any interval from 5 to 100 seconds.

Anesthesia Ventilator, fluidically controlled for less maintenance. Precise and reliable. With a built-in gas evacuator. Ohio can also customize a gas evacuation interface to accommodate your disposal system.

O_2 Monitor with visual and audio alarms.

One system designed to suit all can't really satisfy everyone. Because somewhere along the line you have to compromise. Each of you has your own ideas about how best to provide excellence in patient care in your own operating theater. And each OR has its unique needs.

Most new systems begin with one of the four OHIO® anesthesia machines. Rugged. Practical. Versatile. Functional. Delivering your preference in anesthetic agents with accuracy and safety.

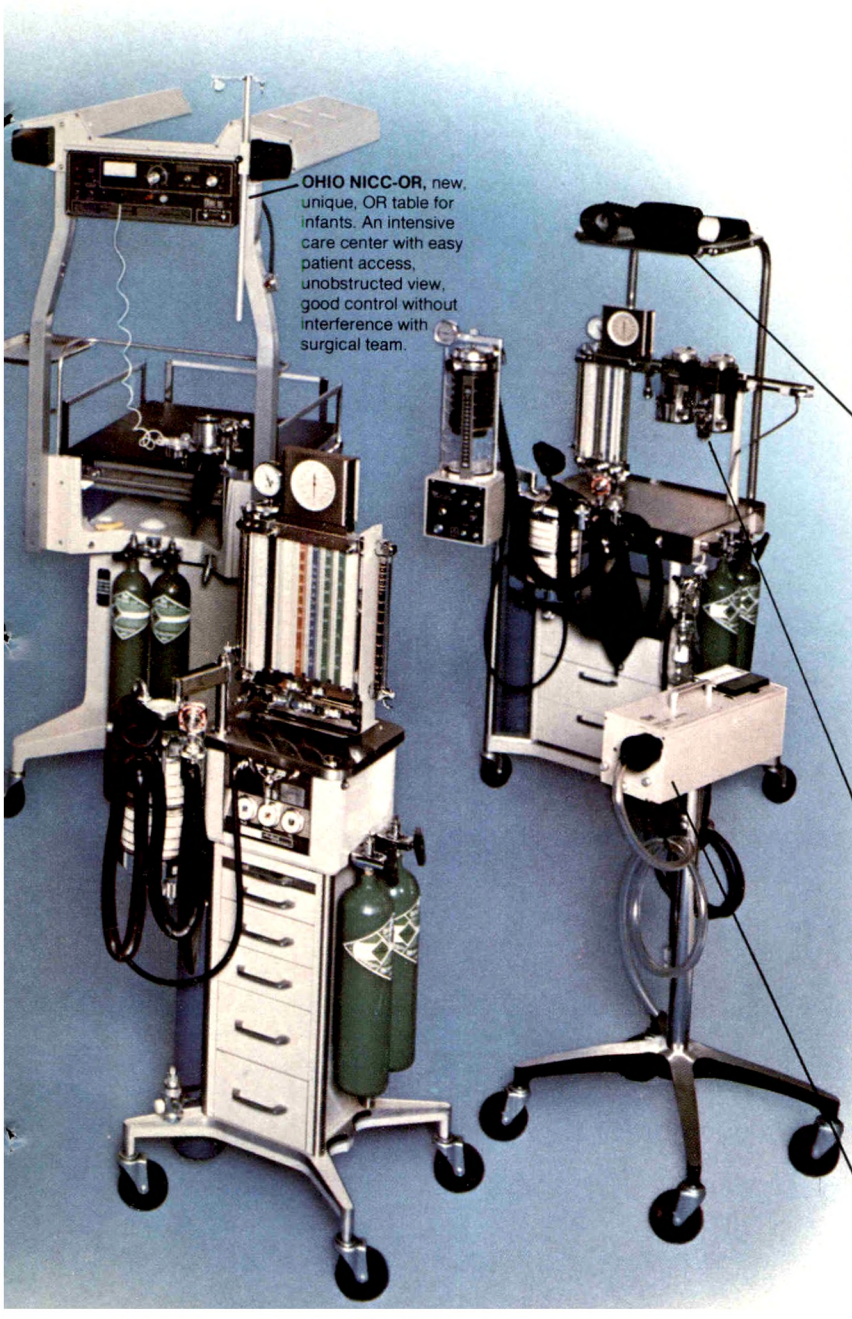
Then, your system grows to support your skills and techniques, as you add accessories and options from Ohio: Vaporizers, ventilators and absorbers, monitors, disposables, medical gases, and gas evacuation systems. And we always have more on the way.

You can depend on over 100 factory-trained Ohio servicemen and six service centers in the U.S. and Canada to keep your anesthesia equipment performing. Plus a knowledgeable sales staff.

Send for information. Or send for your salesman. Ohio will help you develop a reliable, sophisticated anesthesia system. One you can build on when future technologies develop. So, you'll never have to compromise in caring for your patients.

Ohio Medical Products AIRCO®

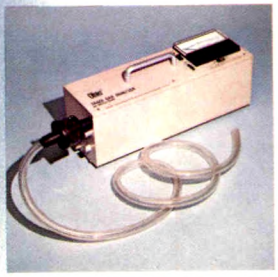
3030 Airco Drive, P.O. Box 7550, Dept. 305
Madison, Wisconsin 53707



OHIO NICC-OR, new, unique, OR table for infants. An intensive care center with easy patient access, unobstructed view, good control without interference with surgical team.

HOPE® II resuscitator with a new valve and the facility to administer enriched oxygen concentrations.

OHIO Calibrated Vaporizer, new, easy-to-use, temperature and flow compensated with excellent low-flow performance.



New Trace Gas Analyzer detects and measures the concentration of nitrous oxide in the operating room atmosphere; alerting OR personnel to leak sources.

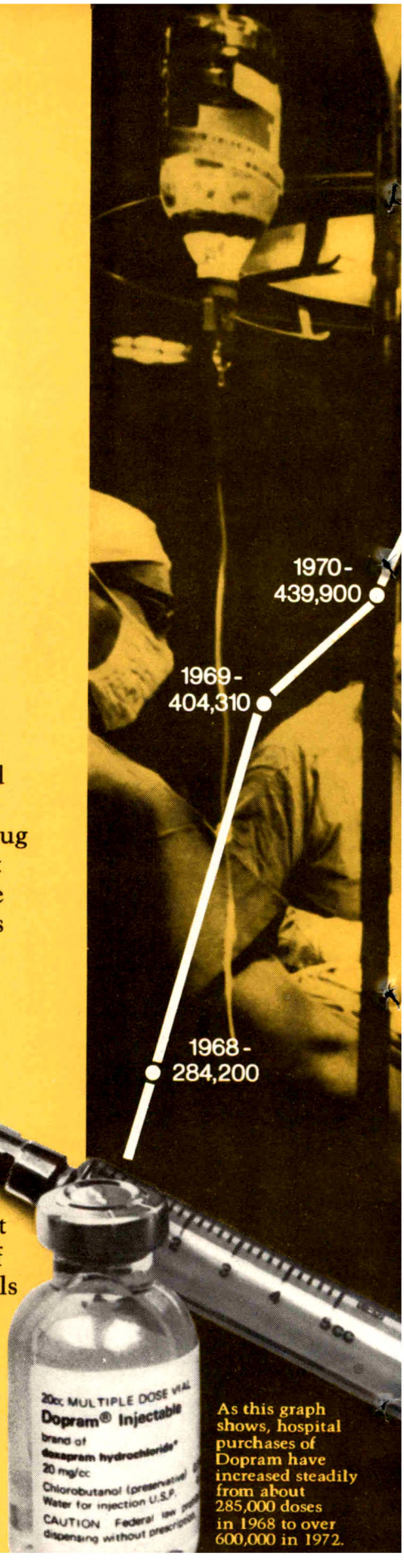
In all types of hospitals across the United States, its usage grows–

Dopram®
Injectable
(doxapram HCl)

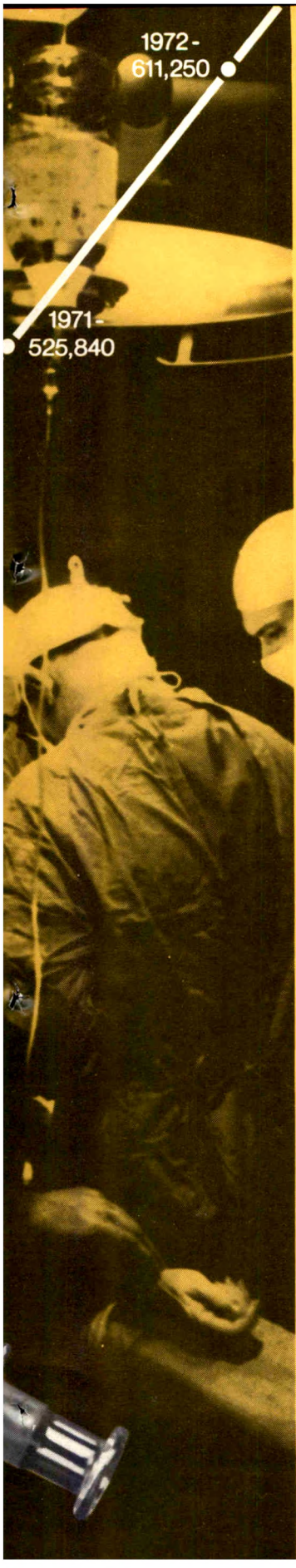
Seven years ago, A. H. Robins introduced Dopram, a unique respiratory stimulant developed in the company's research laboratories. What made this drug so useful to the anesthesiologist was its ability to rapidly restore the respiratory drive in patients with drug-induced post anesthetic depression.

Usage of Dopram has been steadily increasing each year, until today it has become a very important drug in the armamentarium of more than 1,500 hospitals of all types in all 50 states, the District of Columbia, and a number of foreign countries. These hospitals purchased more than 600,000 doses in 1972 alone.

Dopram–an important drug in anesthesiology. Try it for sighs!



As this graph shows, hospital purchases of Dopram have increased steadily from about 285,000 doses in 1968 to over 600,000 in 1972.



Indications

1. To stimulate respiration in patients with drug induced post-anesthetic respiratory depression or apnea other than that due to muscle relaxant drugs.
2. To pharmacologically stimulate deep breathing in the so-called "stir-up" regimen in the post-operative patient. Simultaneous administration of oxygen is desirable.
3. To hasten arousal and return of protective pharyngeal and laryngeal reflexes.
4. To aid in the differential diagnosis of post-anesthetic respiratory depression. Failure to adequately stimulate respiration suggests residual muscle relaxant effect.
5. To stimulate respiration, hasten arousal and to encourage the return of laryngopharyngeal reflexes in patients with mild to moderate respiratory and CNS depression due to drug overdosage.

Contraindications—Epilepsy and other convulsive states: incompetence of the ventilatory mechanism due to muscle paresis, flail chest, pneumothorax, airway obstruction, and extreme dyspnea; severe hypertension and cerebrovascular accidents; hypersensitivity.

Doxapram is not recommended for patients 12 years of age or under because studies to evaluate its safety and efficacy have not been performed.

Warnings—Doxapram is an analeptic agent; it is neither an antagonist to muscle relaxant drugs nor a specific narcotic antagonist. Since doxapram has an acid pH, it should not be mixed with alkaline solutions such as thiopental sodium.

Since narcosis may recur after stimulation with doxapram, care should be taken to maintain close observation until the patient has been fully alert for 1/2 to 1 hour. (Duration of drug 5-12 minutes.)

Doxapram is an adjunct to well-accepted supportive measures and resuscitative techniques. It may not stimulate adequate spontaneous breathing or provide sufficient arousal in patients who are severely depressed with CNS depressant drugs.

When doxapram is administered to postoperative patients or to patients in a state of narcosis with chronic pulmonary insufficiency, oxygen should be administered concomitantly. Failure to do so may result in further oxygen debt and more severe dyspnea due to the increased work of breathing.

Doxapram should be administered with great care and only under close supervision to patients with cerebral edema, bronchial asthma, severe tachycardia, cardiac arrhythmia, cardiac disease, hyperthyroidism and pheochromocytoma.

Usage in pregnancy

No adequate clinical studies have been performed to determine the safe use of doxapram in pregnancy. Until further clinical experience has been obtained, the physician must weigh the need against possible risks in using the drug in pregnant patients or in women of child-bearing potential.

Precautions—Recommended dosages of doxapram should be employed and maximum total dosages should not be exceeded. In patients with advanced pulmonary disease with hypoxemia, marked respiratory stimulation increases the work of breathing and may, thus, increase oxygen consumption and carbon dioxide production.

With excessive dosage, hyperventilation induced by doxapram may lead to respiratory alkalosis and hypocapnia with tetany and, theoretically, apnea.

An adequate airway is essential. In order to avoid side effects, it is advisable to use the minimum effective dosage. Monitoring of the blood pressure and deep tendon reflexes is recommended to prevent overdosage.

It is desirable that blood gases (P_{O_2}, P_{CO_2} O_2 saturation) be monitored to assess the effectiveness of respiratory stimulation.

Intravenous barbiturates, oxygen and resuscitative equipment should be readily available to manage overdosage manifested by excessive central nervous system stimulation. Slow administration of the drug and careful observation of the patient during administration and for some time subsequently are advisable to insure restoration of the protective reflexes. The possibility of post-stimulation respiratory depression must be kept in mind. In patients who have been lightly curarized, doxapram may temporarily mask the residual effects of muscle relaxant drugs.

Doxapram should be administered cautiously to patients receiving sympathomimetic or monoamine oxidase inhibiting drugs, since a synergistic pressor effect may occur. It should likewise be used with care in post-operative patients with marked dyspnea due to obstructive pulmonary emphysema, acute or chronic asthma, profound metabolic disorders, severe to moderately severe hypertension, increased cerebrospinal fluid pressure, head injury and acute agitation.

Since doxapram may stimulate basal gastric secretion, it should be used with care in patients with peptic ulcer disease and in patients undergoing gastric surgery.

Vascular extravasation or use of a single injection site over an extended period should be avoided since either may lead to thrombophlebitis.

Hypocapnia accompanying forced ventilation is a potent stimulus to cerebral vasoconstriction; it may be postulated that some element of risk may exist from reduced cerebral blood flow following prolonged and intensive hyperventilation.

Since an increase in epinephrine release has been noted with doxapram, it is recommended that initiation of therapy with this respiratory stimulant be delayed for at least 10 minutes following the discontinuance of anesthetics known to sensitize the myocardium to catecholamines, such as halothane and cyclopropane.

As with other intravenous preparations, all precautions should be taken during administration of doxapram to insure that injection is made directly into a suitable vein; extravasation, and inadvertent intra arterial injection should be avoided.

Adverse reactions—The following adverse reactions have been reported: *Central and Autonomic Nervous Systems.* Hyperactivit feeling of warmth, sweating, muscle tremor clonus, increased deep tendon reflexes, dizziness, muscle spasticity, pyrexia, confusion, paresthesia, pupillary dilatation pilomotor erection, headache, bilateral babinski, fasciculation and carpopedal spasm. A grand mal seizure occurred 95 minutes after drug administration in a known epileptic patient who was on anticonvulsant medication.

Respiratory. Cough, dyspnea, laryngospasr bronchospasm and hiccough.

Cardiovascular. Hypertension, sinus tachycardia, bradycardia, extrasystoles, lower T-waves, premature ventricular contractions, irregular heart rhythm, tightness in chest. Although a mild to moderate increase in blood pressure is not infrequent, such an increase may occasionally be of concern in hypertensive patients.

Gastrointestinal. Nausea and/or vomiting salivation, stimulation of lower bowel, sour taste.

Genitourinary. Urinary retention, stimulation of urinary bladder with spontaneous voiding.

Miscellaneous. Pruritus, thrombophlebitis

Laboratory Determinations. A decrease in hemoglobin, hematocrit, or red blood cell count has been observed in postoperative patients. In the presence of pre-existing leukopenia, a further decrease in WBC wa observed following anesthesia and treatment with doxapram hydrochloride. Elevation of BUN and albuminuria have been observed.

In some of the cases cited above, the patients had received multiple drugs concomitantly, thus preventing an absolute judgment as to the role of doxapram in these reactions.

Dosage—For complete information concerning dosage and administration see package insert.

Supply—Dopram (doxapram hydrochloride) is available in 20 cc rubber stoppered vials containing 20 mg/cc, with chlorobutanol 0.5% as the preservative.

A. H. Robins Company
Richmond, Virginia 23220

A·H·ROBINS

ANECTINE®
(succinylcholine chloride)
For controlled muscle relaxation adjunctive to anesthesia:

FLO-PACK® for prolonged relaxation

- instant-mix sterile powder interfaces with all major parenteral systems (vacuum or nonvacuum)
- each unit complete—no needle or syringe needed
- retains potency indefinitely
- no refrigeration required
- unbreakable, sterile plastic injection units of 500 and 1,000 mg

INJECTION for short-term relaxation

- a product of choice for intubation and other short procedures
- unique square bottle and bright yellow label for positive identification
- ready for immediate use
- 20 mg per cc . . . in 10 cc multidose vials
- flip-top cap for easy opening
- single or multiple use

ANECTINE®
(succinylcholine chloride)
THE LONG AND SHORT of surgical muscle relaxation

THIS DRUG SHOULD BE USED ONLY BY INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS AND HAZARDS.

DESCRIPTION: Anectine brand Succinylcholine Chloride is an ultra short-acting depolarizing type muscle relaxant. Chemically it is a di-quaternary base consisting of the di-chloride salt of the di-choline ester of succinic acid. It is a white, odorless, slightly bitter powder and very soluble in water. The drug is unstable with alkaline solutions, but relatively stable in acid solutions depending upon the concentration of the solution and the storage temperature. While solutions of succinylcholine chloride are sterilized by autoclaving, they should, nevertheless, be stored under refrigeration to preserve their potency.

INDICATIONS: Succinylcholine chloride is indicated as an adjunct to anesthesia to induce skeletal muscle relaxation. It may be employed to reduce the intensity of muscle contractions of pharmacologically or electrically induced convulsions.

CONTRAINDICATIONS: Succinylcholine is contraindicated for persons with a known hypersensitivity to the drug.

WARNINGS:

WARNING: SUCCINYLCHOLINE SHOULD BE USED ONLY BY THOSE SKILLED IN THE MANAGEMENT OF ARTIFICIAL RESPIRATION AND ONLY WHEN FACILITIES ARE INSTANTLY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND FOR PROVIDING ADEQUATE VENTILATION OF THE PATIENT, INCLUDING THE ADMINISTRATION OF OXYGEN UNDER POSITIVE PRESSURE AND THE ELIMINATION OF CARBON DIOXIDE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR TO CONTROL RESPIRATION.

Succinylcholine should not be mixed with short-acting barbiturates in the same syringe, or administered simultaneously during intravenous infusion through the same needle. Solutions of succinylcholine have an acid pH whereas those of barbiturates are alkaline in reaction. Depending upon the resultant pH of a mixture of solutions of these drugs, either free barbituric acid may be precipitated or succinylcholine hydrolyzed.

Usage in Pregnancy The safe use of succinylcholine has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

PRECAUTIONS: Low levels of, or abnormal variants of plasma cholinesterase may be associated with prolonged respiratory depression or apnea following the use of succinylcholine. Low levels of plasma cholinesterase may occur in patients with severe liver disease or cirrhosis, severe anemia, malnutrition, severe dehydration, changes in body temperature, exposure to neurotoxic insecticides or those receiving antimalarial drugs. Succinylcholine should be administered with extreme care to such patients and dosage should be minimal. If low plasma cholinesterase activity is suspected, a small test dose of from 5 to 10 mg of succinylcholine may be administered, or relaxation may be produced by the cautious administration of a 0.1% solution of the drug by intravenous drip. Drugs which either inhibit plasma cholinesterase, such as neostigmine or phospholine iodide, or compete with succinylcholine for the enzyme, as does intravenous procaine, should not be given concurrently with succinylcholine.

Succinylcholine should be administered with great caution to patients with severe burns, those recovering from severe trauma, those suffering from electrolyte imbalance, those receiving quinidine, those who have been digitalized recently or who may have digitalis toxicity as serious cardiac arrhythmias or cardiac arrest may result. Great caution should be observed also in patients with pre-existing hyperkalemia or who are paraplegic, have suffered spinal neuraxis injury, or have degenerative or dystrophic neuromuscular disease, as such patients tend to become severely hyperkalemic when succinylcholine is given.

When succinylcholine is given over a prolonged period of time, the characteristic depolarization block of the myoneural junction may change to a non-depolarizing block which results in prolonged respiratory depression or apnea. Under such circumstances, small repeated doses of neostigmine may possibly act as an antagonist. A peripheral nerve stimulator (e.g., the Wellcome Peripheral Nerve Stimulator) may be used to ascertain the type of neuromuscular blockade. If a depolarization block is present both fast (tetanic) and slow (twitch) rates of nerve stimulation are well sustained, and post-tetanic facilitation is absent. If a non-depolarizing block is present there is post-tetanic facilitation and "fade" of successive stimuli on both fast (tetanic) and slow (twitch) rates of nerve stimulation.

Succinylcholine should be used with caution during ocular surgery and in patients with glaucoma. The drug should be employed with caution in patients with fractures or muscle spasm as the muscle fasciculations may cause additional trauma. Muscle fasciculations and hyperkalemia may be reduced by administering a small dose of a non-depolarizing relaxant. If other relaxants are to be used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered.

During the past few years, reports have called attention to a fulminant syndrome, malignant hyperthermia, observed during anesthesia. Its etiology is not fully understood. Malignant hyperthermia occurs in genetically prone individuals of all ages and both sexes receiving potent anesthetics such as halothane, methoxyfluothane, cyclopropane and diethyl ether. It appears to develop irrespective of the concomitant use of a muscle relaxant, but may be triggered by succinylcholine. Because of the seriousness of this syndrome and the need for early effective treatment of the patient, it is suggested that the continuous monitoring of the temperature will serve as an aid to the early recognition of malignant hyperthermia.

ADVERSE REACTIONS: Adverse reactions consist primarily of an extension of the drug's pharmacological actions. Profound and prolonged muscle relaxation may occur, resulting in respiratory depression to the point of apnea. Hypersensitivity to the drug may exist in rare instances.

The following adverse reactions have been reported: bradycardia, tachycardia, hypertension, hypotension, arrhythmias, cardiac arrest, prolonged respiratory depression or apnea, hyperthermia, increased intraocular pressure, muscle fasciculation, postoperative muscle pain, myoglobinemia and excessive salivation.

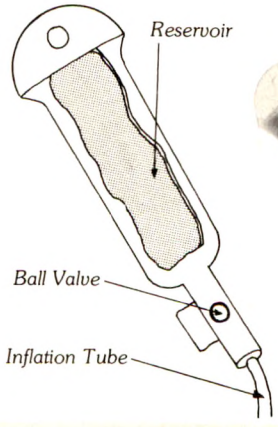
MANAGEMENT OF ADVERSE REACTIONS: Apnea or prolonged muscle paralysis should be treated with controlled respiration.

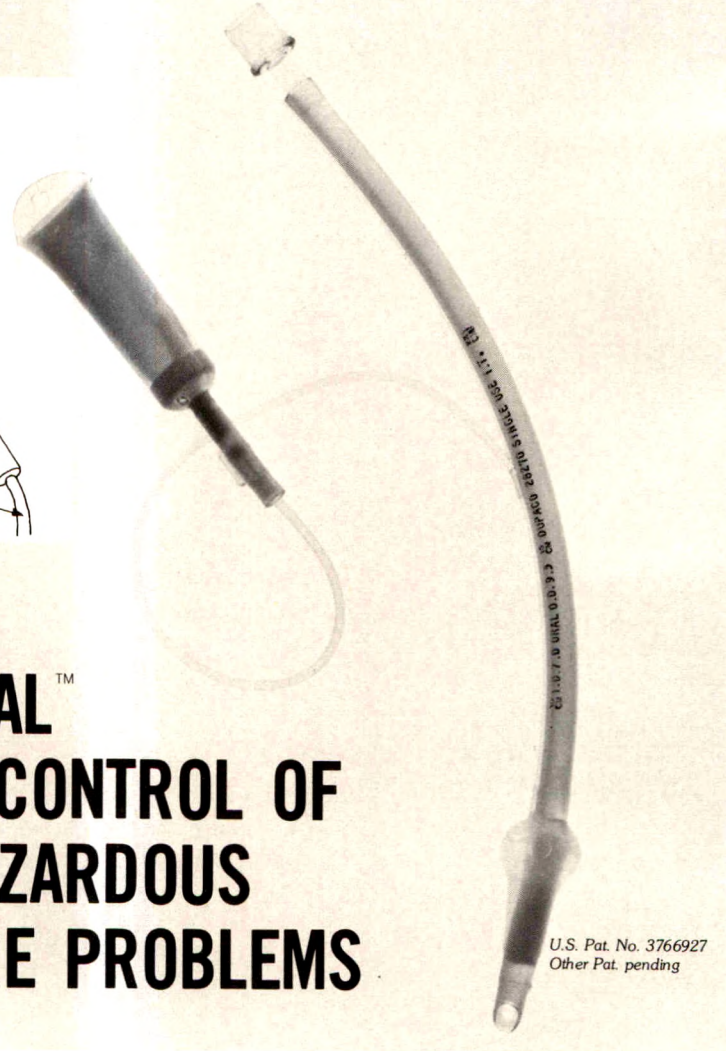
The use of neostigmine to reverse a non-depolarization block is a medical decision which must be made upon the basis of the individual clinical pharmacology and the experience and judgment of the clinician. When neostigmine is used atropine should also be administered.

SUPPLIED: Injection, Multi-dose vials, 20 mg cc, 10 cc, boxes of 12 vials. Flo-Pack® Sterile Powder 500 mg and 1,000 mg, boxes of 12.

Complete literature available on request from Professional Services Dept. PML.

Wellcome
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709





LIQUI-SEAL™ ALLOWS CONTROL OF MOST HAZARDOUS PRESSURE PROBLEMS

U.S. Pat. No. 3766927
Other Pat. pending

Dupaco's new Liqui-Seal™ Systems solves pressure problems associated with air filled Tracheal Tube cuffs by eliminating air itself. This is accomplished by filling the cuff with saline solution from a self-contained reservoir. Since the fluid in the cuff system is incompressable, as compared with air, the pressure on the tracheal mucosa will vary directly with the height of the top of the fluid reservoir above the cuff at the time the cuff inflation valve is closed. The use of Liqui-Seal™ System gives the following advantages:

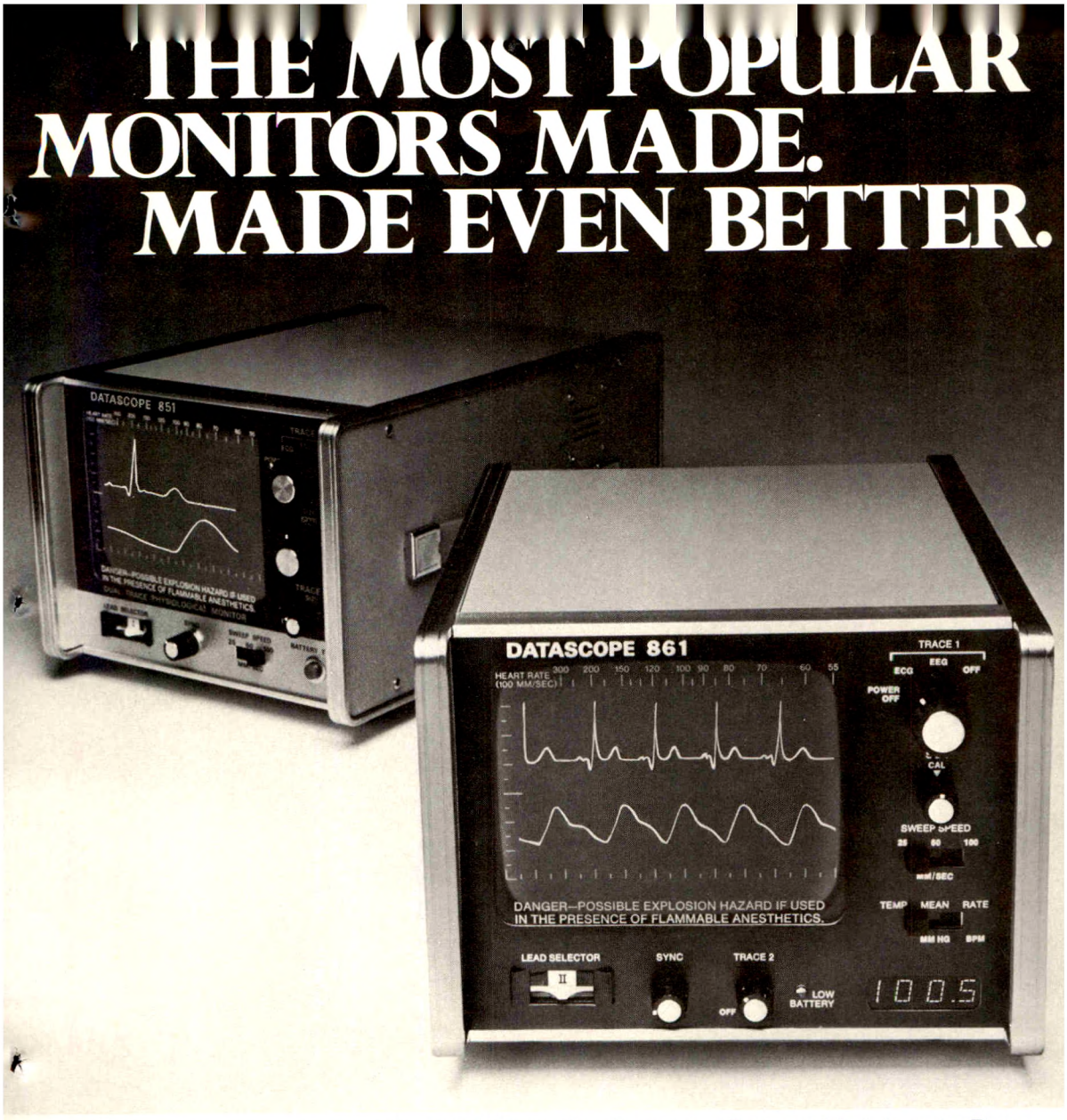
1. Positive seal at extremely low pressure.
2. Safe for prolonged use without periodic cuff deflation.
3. Cuff pressure readily regulated.
4. Cuff pressure constant during N_2O anesthesia.
5. No change in cuff pressure due to altitude changes (air evacuation).
6. Maximum pressure obtainable approx. 40cm H_2O.
7. One hand operation.

Liqui-Seal™ Tracheal Tubes are available in five sizes, have Murphy eye and are sterile packaged in convenient peel packages with appropriate connector.

DUPACO
INCORPORATED

P.O. Box 98, San Marcos, CA 92069

THE MOST POPULAR MONITORS MADE. MADE EVEN BETTER.



For some time now, our monitors have been selected for use in surgery by more medical people than any other battery-powered monitors in the world. Because we give you more of what you want in a monitor than any other monitors in the world.

However, this didn't stop us from improving them.

Our new Datascope 851 and 861 will now give you heart rate not only from ECG, but also from pulse or blood pressure.

And both monitors will give you 2 traces. So you can monitor ECG (or EEG) and pulse simultaneously.

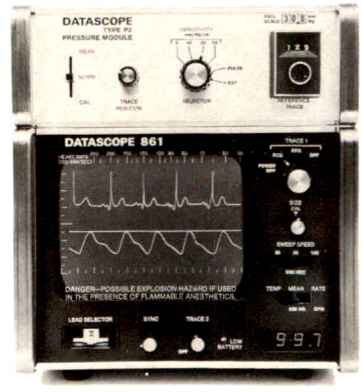
And both give you beat by beat synchronization†. So a single ECG complex shows up with each full sweep.

The 861 does even more. It monitors body temperature. On a digital read-out. And this same digital display will give you heart rate when you want it; or mean blood pressure when you are using the 861 with our Pressure Module.

For all the things our 851 and 861 do, they're surprisingly portable. And they offer longer battery-operating time than any other monitors. In some cases, actually twice as long.

Will they continue to be the most popular monitors made? More so.

For further information about our new 851, 861, or our Pressure Module, write Datascope Corp., 580 Winters Ave., Paramus, NJ 07652.



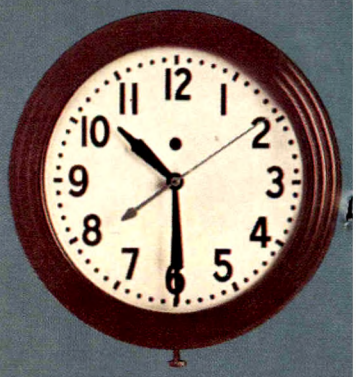
The 861 with Pressure Module.

THE DATASCOPE 851/861

†U.S. PATENT NO. 3457452

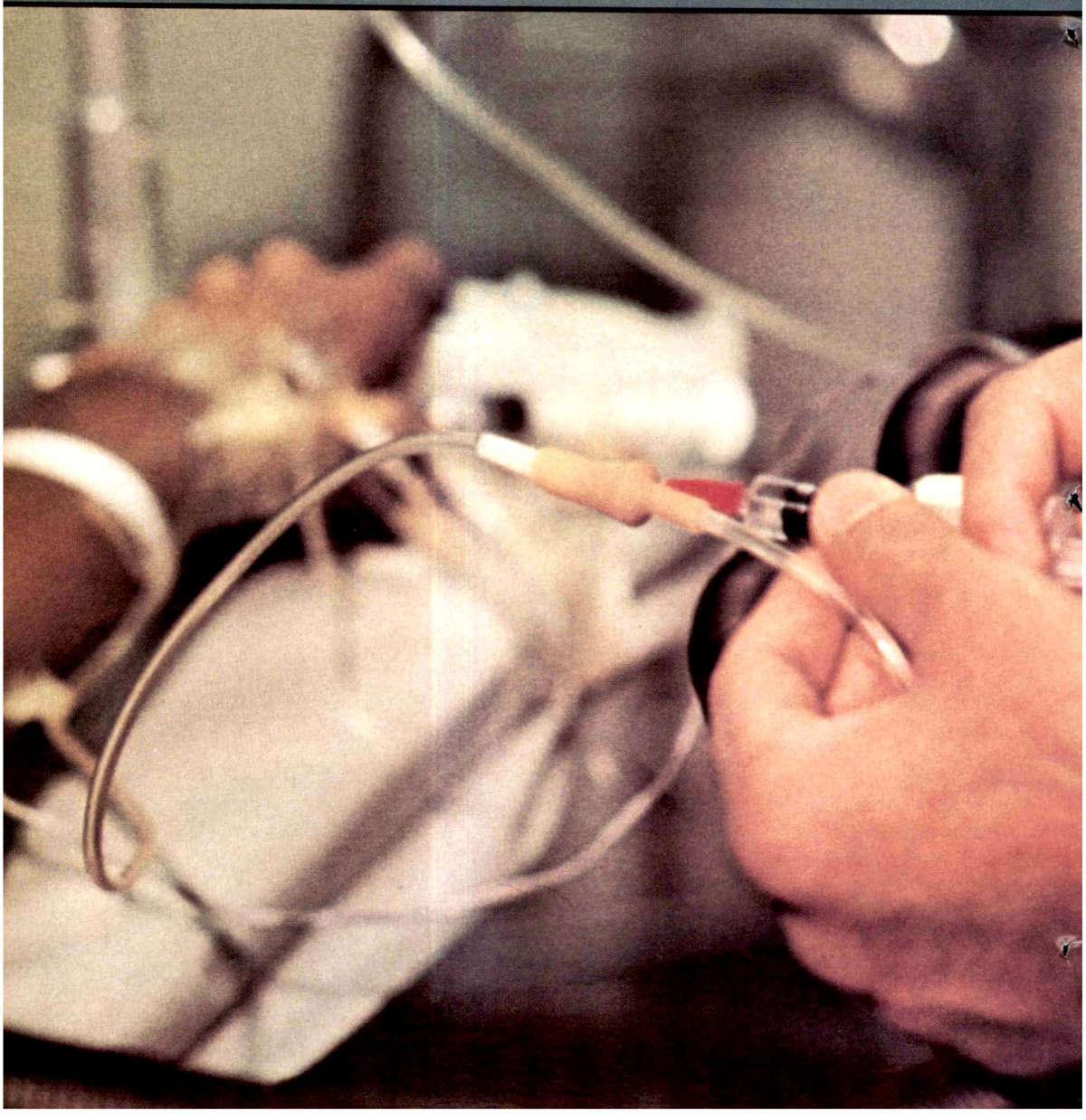
SUBLIMAZE® (fentanyl) has a uniquely short duration of analgesic action—for more precise control and minimal risk of prolonged narcotic effects.

Within 5 minutes I.V., SUBLIMAZE® (fentanyl) reaches its peak analgesic effect.



Within 30 to 60 minutes I.V., the analgesic effect of SUBLIMAZE® (fentanyl) is almost completely dissipated.†

† Respiratory depressant effects may last longer than the analgesia and are increased and prolonged with larger doses, multiple doses or use of postoperative narcotic analgesics.



For potent narcotic analgesic action with rapid onset and short duration:

SUBLIMAZE fentanyl provides profound analgesia without hypnosis and with little or no sedation. With this analgesia as a foundation, it is possible to use light general anesthesia in most cases.

SUBLIMAZE fentanyl is particularly suited for maintenance of analgesia after INNOVAR® injection* has been used for induction. It may also be used preoperatively, during surgery with any common general or regional anesthetic agent, and in the immediate postoperative period whenever the need for potent analgesic action arises.

SUBLIMAZE fentanyl is available both alone and as a component of INNOVAR injection.*

*INNOVAR injection is composed of a 50:1 mixture of droperidol 2.5 mg./cc. and fentanyl 0.05 mg./cc., with lactic acid for adjustment of pH to 3.5 ± 0.3.

SUBLIMAZE® (fentanyl) offers:

☐ Almost immediate analgesia—peak effect within 5 minutes I.V., 8 minutes I.M.

☐ Short duration of analgesic action—30 to 60 minutes with a single I.V. dose of up to 0.1 mg. (Respiratory depressant effects may las longer than the analgesia and are increased an prolonged with larger doses, multiple doses or use of postoperative narcotic analgesics.)

☐ No evidence of liver, heart, or kidney toxicity—expecially valuable in poor-risk patients However, the drug should be administered cautiously in the presence of liver or kidney dysfunction or cardiac arrhythmias, and the dose should be appropriately reduced in poor-risk patients.

☐ Immediate reversibility by narcotic antagonists.

☐ Little or no histamine release—decreasing the risk of cardiovascular instability.

☐ Minimal emetic effect—has been used successfully to prepare nonfasting patients for awake intubation.

☐ Prevention or reversal of emergence delirium and tachypnea.

SUBLIMAZE® Ⓒ (fentanyl) injection

0.05 mg./cc. as the citrate.
Warning: May be habit forming.
Sodium hydroxide for adjustment of pH to 4.0—7.5

INNOVAR® injection and SUBLIMAZE® (fentanyl) injection are available for use only upon direction of a physician. For information relating to Contraindications, Warnings, Precautions and Adverse Reactions for SUBLIMAZE fentanyl, please turn page.

© McNeil Laboratories, Inc., 1974

SUBLIMAZE® (fentanyl) injection

Description
Each cc. contains:
Fentanyl as the citrate ..... 0.05 mg.
Warning—May be habit forming.
Sodium hydroxide for adjustment of pH to 4.0-7.5
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY.

Actions SUBLIMAZE fentanyl is a narcotic analgesic with actions qualitatively similar to those of morphine and meperidine. SUBLIMAZE fentanyl in a dose of 0.1 mg. (2.0 cc.) is approximately equivalent in analgesic activity to 10 mg. of morphine or 75 mg. of meperidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. SUBLIMAZE fentanyl appears to have less emetic activity than other narcotic analgesics. Histamine assays and skin wheal testing in man, as well as *in vivo* testing in dogs, indicate that histamine release rarely occurs with SUBLIMAZE fentanyl.

SUBLIMAZE fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. It may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia, and bronchoconstriction.

The onset of action of SUBLIMAZE fentanyl is almost immediate when the drug is given intravenously; however, maximal analgesic and respiratory depressant effect may not be noted for several minutes. The average duration of action of the analgesic effect is 30 to 60 minutes. Following intramuscular administration, the onset of action is from seven to eight minutes, and the duration of action is from one to two hours.

Although the duration of the respiratory depressant effect is unknown, as with other narcotic analgesics it may be considerably longer than the analgesic effect.

Indications SUBLIMAZE fentanyl is indicated:
—for analgesic action of short duration during the anesthetic periods, premedication, induction, and maintenance, and in the immediate postoperative period (recovery room) as the need arises.
—for use as a narcotic analgesic supplement in general or regional anesthesia.
—for administration with a neuroleptic such as INAPSINE® (droperidol) injection as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.

Contraindications SUBLIMAZE fentanyl is contraindicated in patients who are hypersensitive to the drug.

Warnings PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* FENTANYL SHOULD HAVE APPROPRIATE SURVEILLANCE.

RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

If SUBLIMAZE fentanyl is administered with a tranquilizer such as INAPSINE droperidol, the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE fentanyl persists longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as 1/4 to 1/3 those usually recommended. A neuromuscular blocking agent compatible with the patient's condition may be required to control muscle rigidity which may develop with the use of SUBLIMAZE fentanyl.

Drug Dependence: SUBLIMAZE fentanyl can produce drug dependence of the morphine type and therefore has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE fentanyl in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure: SUBLIMAZE fentanyl should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition, SUBLIMAZE fentanyl may obscure the clinical course of patients with head injury.

Usage in Children: The safety of SUBLIMAZE fentanyl in children younger than two years of age has not been established.

Usage in Pregnancy: The safe use of SUBLIMAZE fentanyl has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

Precautions *The initial dose of SUBLIMAZE fentanyl should be appropriately reduced in elderly, debilitated and other poor risk patients. The effect of the initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms (see Actions) SUBLIMAZE fentanyl can also alter respiration. When SUBLIMAZE fentanyl is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia. When used with a tranquilizer such as INAPSINE droperidol, blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE fentanyl should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Postoperatively, respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists (levallorphan, nalorphine, and naloxone; consult individual prescribing information before using). Should respiration be compromised by muscle rigidity, assisted or controlled respiration and possibly a neuromuscular blocking agent will be required. The occurrence of muscle rigidity is related to the speed of intravenous injection and the incidence can be reduced by slow intravenous injection.

When a tranquilizer such as INAPSINE droperidol is used with SUBLIMAZE fentanyl, pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE fentanyl. When patients have received such drugs, the dose of SUBLIMAZE fentanyl required will be less than usual. Likewise, following administration of SUBLIMAZE fentanyl the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE fentanyl should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE fentanyl may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE fentanyl should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE fentanyl is used with a tranquilizer such as INAPSINE droperidol, hypotension can occur. If this occurs the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of INAPSINE droperidol, epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE droperidol.

Adverse Reactions As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE fentanyl are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur.

Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

When a tranquilizer such as INAPSINE droperidol is used with SUBLIMAZE fentanyl, the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with antiparkinson agents. Postoperative drowsiness is also frequently reported following the use of INAPSINE droperidol.

Overdosage ***Manifestations:*** The manifestations of SUBLIMAZE fentanyl overdosage are an extension of its pharmacologic actions.
Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan, or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. Consult the package insert for the individual narcotic antagonists for details about use.

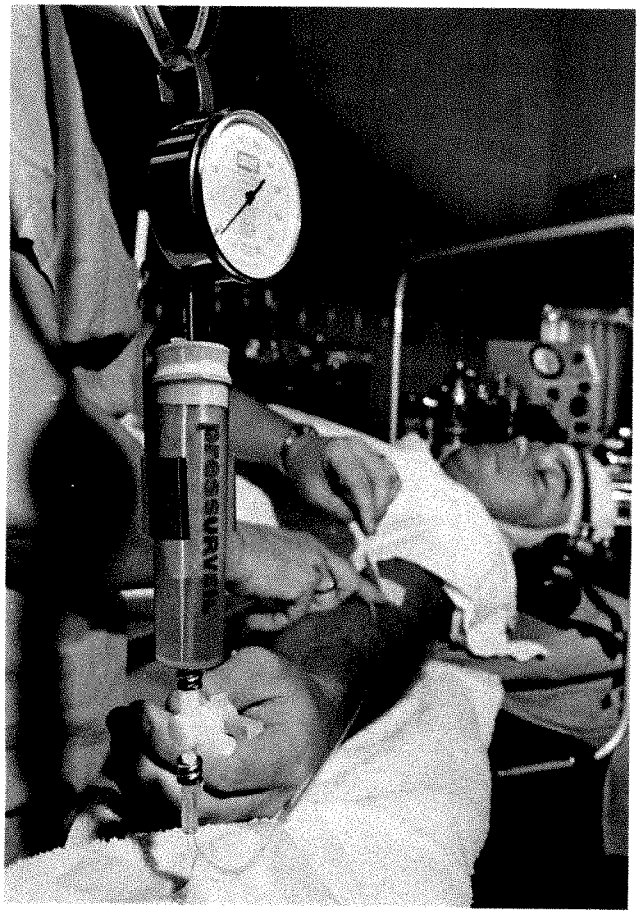
How Supplied SUBLIMAZE® (fentanyl) injection is supplied in 2 cc. (**NDC** 0045-0180-03) and 5 cc. (**NDC** 0045-0180-05) ampuls, in packages of 12.

IMPORTANT: Complete dosage information is available in insert which accompanies each package (or on request). The drug is available only upon direction of a physician.
U.S. Patent No. 3,164,600

9/74

McNEIL McNeil Laboratories, Inc.
Fort Washington, Pa. 19034

What's even easier than Pressurveil™ for continuous blood pressure monitoring? The Pressurveil Kit.



Cat. No. 6700	PRESSURVEIL	$50 box of 10
Cat. No. 6710	Venous Pressure Gauge (0-50 cm H_2O)	$65 each
Cat. No. 6715	Mean Arterial Gauge (20-300 mm Hg)	$45 each
Cat. No. 6720	Dual Reading Gauge for CVP, PAP, PWP (0-45 mm Hg or 0-60 cm H_2O)	$69 each
Cat. No. 6725	**PRESSURVEIL Kit**	**$75 box of 10**

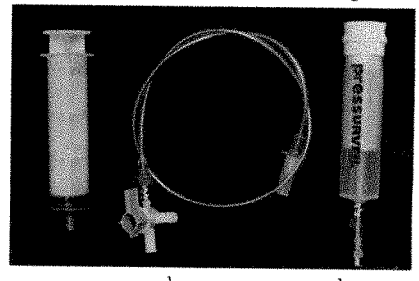
We put ideas to work.

12707 U.S. Highway 19 South
Clearwater, Florida 33516

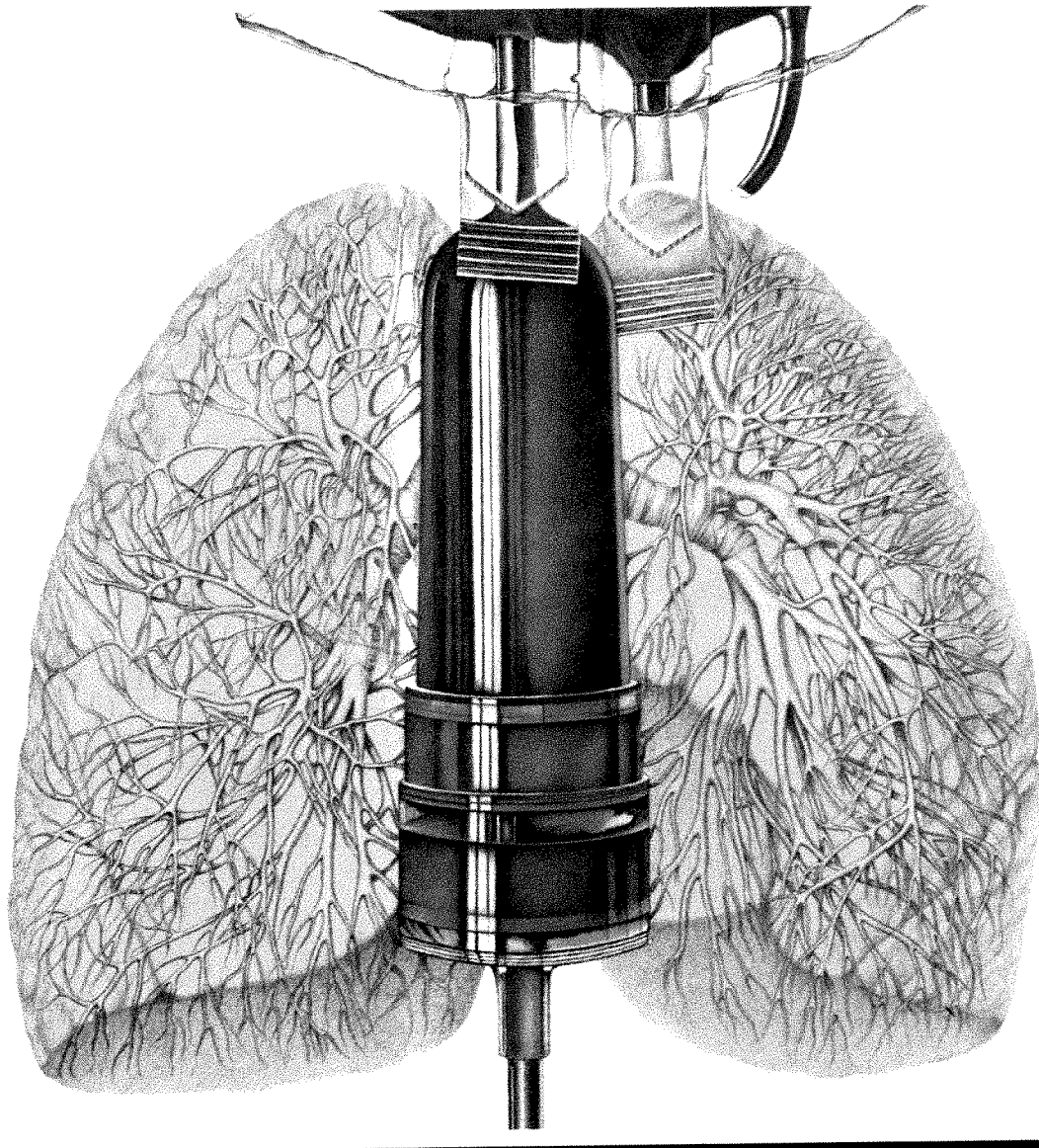
concept INC.

We put an idea to work.

To make your job even easier, we've packaged PRESSURVEIL in a convenient, three-piece disposable kit. Included is the PRESSURVEIL unit, a syringe and a connecting tube with stopcock. It's all in one place. Sterile. Ready-to-use. Just follow the simple instructions. In seconds, you can select the proper gauge and begin monitoring blood pressure continuously, with confidence — whether it's central venous, mean arterial, pulmonary



mean or pulmonary wedge pressure. And, since PRESSURVEIL is portable, you can monitor patients regardless of where they are, or where they're going. PRESSURVEIL minimizes danger of alignment shift and eliminates electric shock hazard. You probably know that with PRESSURVEIL, reliable, continuous blood pressure surveillance is easy. Now, the PRESSURVEIL KIT makes it even easier.



For routine filtration of stored blood the Swank Transfusion Filter, utilizing the principle of Dacron® wool filtration, offers these important advantages:

- **Removes Microaggregates Down to 10-Micron Range**—the vast majority of the amorphous debris in stored blood is less than 30 microns in diameter and will not be removed by a standard screen filter.
- **Adsorptive Filtration**—highly efficient—degenerative blood elements are inherently adhesive and adhere to the Dacron wool fibers.
- **Flow Rate**—the Swank Transfusion Filter will efficiently remove microemboli from stored blood at a flow rate greater than 100cc per minute under gravity.
- **Multiple Unit Capacity**—the Swank Transfusion Filter will maintain efficiency through multiple-unit usage. The exact number of units will vary with blood age.

Now available: Swank Transfusion Filter with integral administration set.

Marketed by

extracorporeal

Extracorporeal Medical Specialties, Inc

Royal & Ross Rts. King of Prussia, Pa. 19406 U.S.A. 215 337 2400

In Europe write:
Extracorporeal S.A., 293 Avenue Winston Churchill, 1180 Brussels, Belgium

When you need to know

DINAMAP for **non-invasive,** routine monitoring of arterial pressure.‡

Using: An ordinary pressure cuff with no transducer. Easily attached to any limb.*

Provides: Automatic determination and digital display of mean arterial pressure.

Write or call for your demonstration.

Applied Medical Research
6 Columbia Drive
Tampa, Fla. 33606
(813) 251-8390 Dept. 3

‡Audible pulse monitor optional.
*Including patient preferred ankle

PI Peripheral Nerve Stimulator

Monitors Muscle Relaxants

The PI Peripheral Nerve Stimulator monitors effects of skeletal muscle relaxants on the neuromuscular junction, detects abnormal response to muscle relaxants and distinguishes between depolarizing and non-depolarizing blockade.

Model NS-2

The NS-2 is now in use in many hospitals throughout the U. S. and abroad. It is designed primarily for use during surgery and delivers stimuli automatically at 5-second intervals. One or fifty pulses-per-second may be selected by momentary push-button switches. Output is a monophasic square wave pulse. Amplitude of the pulse is linearly adjustable. A flashing red light indicates low battery voltage. The NS-2 is solid state, rugged, battery powered, portable and lightweight.

Model NS-3

The NS-3 represents the latest in solid state technology. Use of integrated circuits has made it possible to build a very compact and versatile stimulator. Its miniature size makes the NS-3 more convenient for preoperative and postoperative testing. It delivers stimili at one second intervals when the rocker switch is depressed to the TWITCH position. A fifty-pulses-per-second rate may be selected by depressing the rocker switch to the momentary TETANUS position. Output is a monophasic square wave pulse. Amplitude of the pulse is linearly adjustable. The NS-3 also has a low-battery-voltage indicator.

Professional Instruments Company

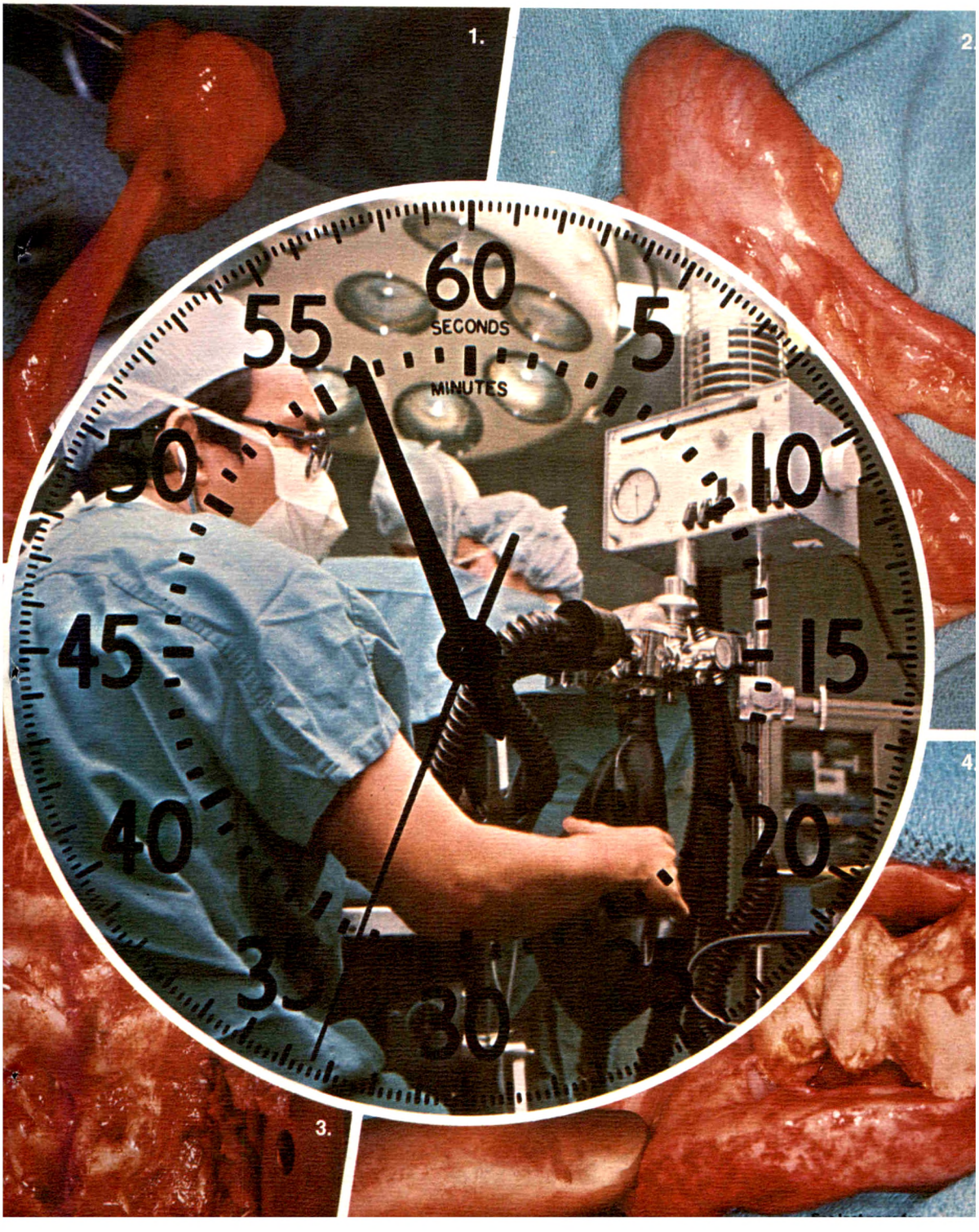
General Office and Sales
Brookhollow Plaza, Suite C-5, 4800 W. 34th Street
P.O. Box 38245, Houston, Texas 77092
Telephone: 713/681-1362

Professional Medical and Scientific Instrumentation

If the Procedure Takes 40 Minutes or More...

You Can Proceed with PAVULON®

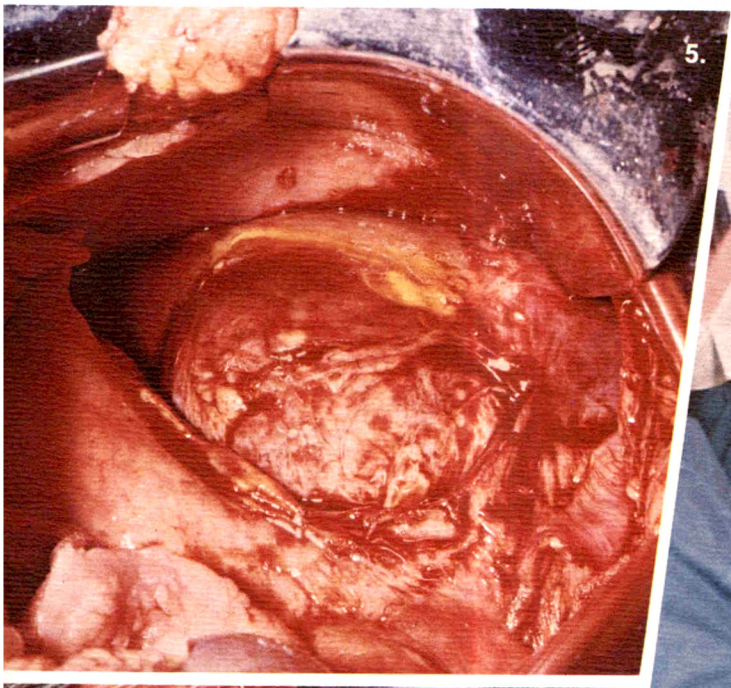
pancuronium bromide

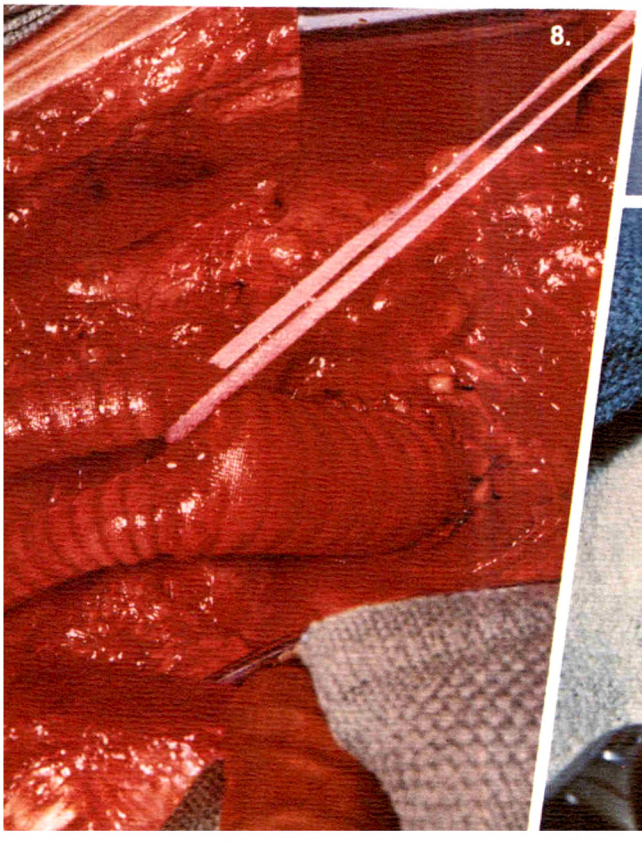


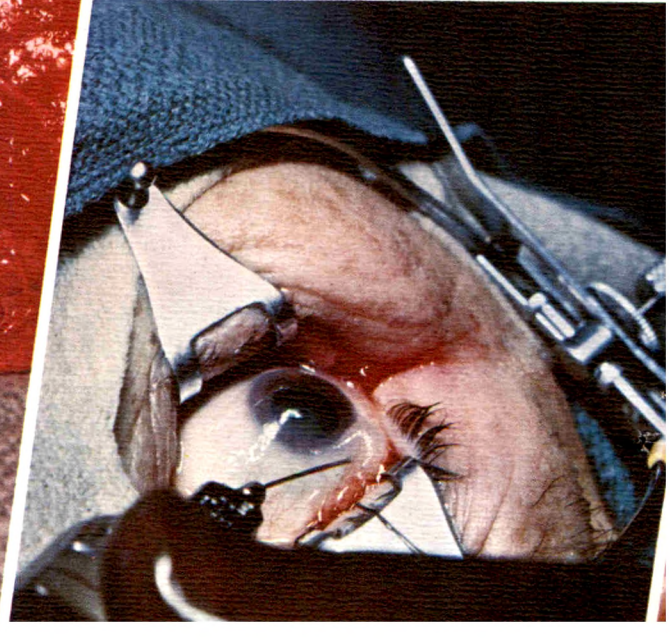
Proceed with PAVULON

pancuronium bromide

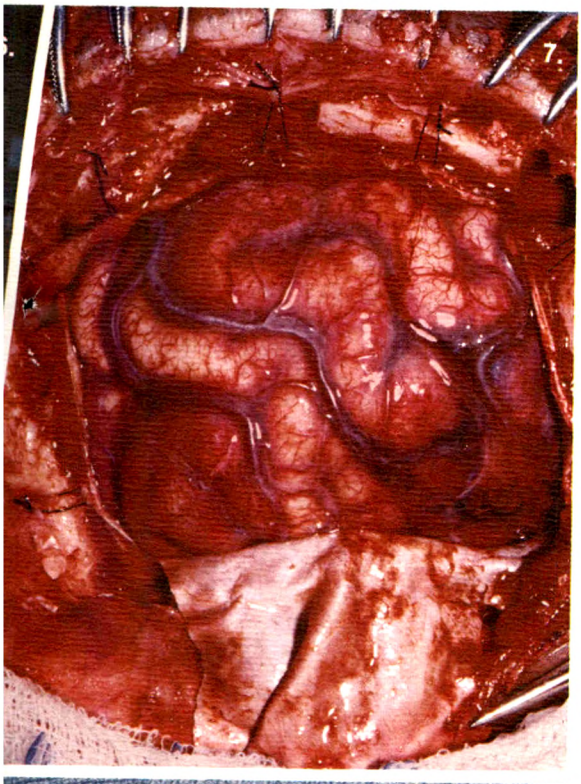
for optimal neuromuscular blockade

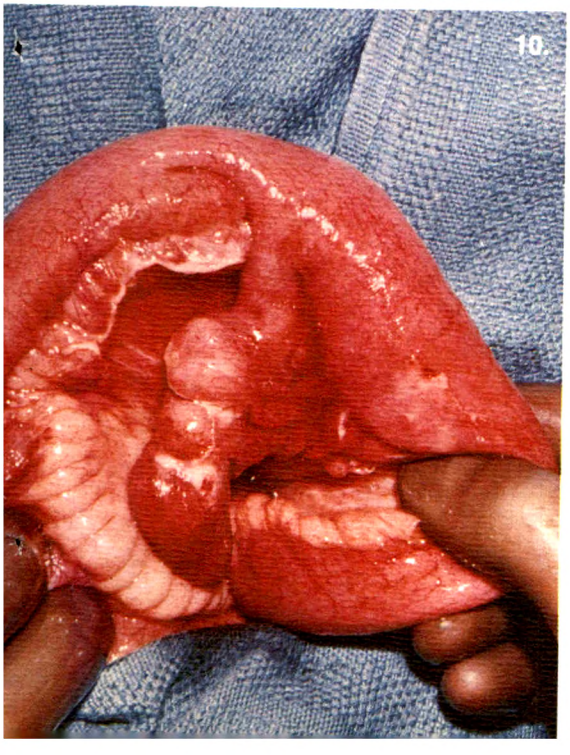






No matter where the surgeon's incision





—whatever the part of the body, or the age of the patient, or the cause of surgery, or the system or systems involved —there's a good chance that Pavulon can provide easy, uncomplicated, optimal, neuromuscular blockade.

Initial doses of Pavulon, given to facilitate endotracheal intubation, take effect in approximately 45 seconds and reach their peak at about 2-3 minutes. Once effective blockade is established, it can be maintained with incremental doses of 1 mg or less.

Pavulon is well tolerated, even in the very old, the very young and the very fragile. Histamine release rarely, if ever, occurs; there is little, if any, ganglionic blockade and little effect upon the circulatory system other than an occasional slight rise in pulse rate and blood pressure. There is no muscle pain, no known effects on consciousness, pain threshold or cerebration.

With proper procedure, reversal of Pavulon is relatively simple and generally uneventful. An appropriate antagonist, such as pyridostigmine bromide, can be used. With adequate dosage of the reversal agent, there is relatively little risk of recurarization. In cases of prolonged respiratory depression, other factors (drug interaction, acidosis, hypokalemia, etc.) should be considered.

KEY: ***1.*** *Polypectomy* ***2.*** *Appendectomy* ***3.*** *Spinal fusion* ***4.*** *Nephrolithotomy* ***5.*** *Open heart surgery* ***6.*** *Cesarean section* ***7.*** *Craniotomy* ***8.*** *Aortic-femoral graft* ***9.*** *Cataract removal* ***10.*** *Diverticulectomy (Meckel's)*

Please see last page of advertisement for complete prescribing information.

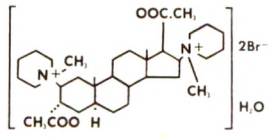
Proceed with PAVULON®

pancuronium bromide

clinically proven nondepolarizing muscle relaxant

THIS DRUG SHOULD ONLY BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: Pavulon (pancuronium bromide) is the aminosteroid 2 beta, 16 beta-dipiperidine-5 alpha-androstane-3 alpha, 17-beta-diol diacetate dimethobromide. It has the following structural formula:



ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon is approximately 5 times as potent as d-tubocurarine chloride.

The onset and duration of action of Pavulon is dose dependent. With the administration of 0.04 mg. per kg. the onset of action, as measured by a peripheral nerve stimulator, is usually within 45 seconds, and its peak effect is usually within 4½ minutes; recovery to 90% of control twitch height usually takes place in less than one hour. Larger doses, more suitable for endotracheal intubation, such as 0.08 mg. per kg. of Pavulon have an onset of action of about 30 seconds, and a peak effect within 3 minutes. Supplemental incremental doses of Pavulon, following the initial dose, slightly increase the magnitude of blockade, and significantly increase the duration of the blockade.

Pavulon has little effect upon the circulatory system. The most frequently reported observation is a slight rise in pulse rate.

Human histamine assays, and clinical observations, as well as in *vivo* guinea pig testing, and in *vitro* mast cell testing, indicate that histamine release rarely, if ever, occurs.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

Pavulon has no known effect on consciousness, the pain threshold, or cerebration.

INDICATIONS: Pavulon is indicated as an adjunct to anesthesia to induce skeletal muscle relaxation. It may also be employed to facilitate the management of patients undergoing mechanical ventilation.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane. No increase in intensity of blockade or duration of action of Pavulon is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. The dosage information which follows has been derived from dose-response studies based on body weight and is intended to serve as a guide only. Since potent inhalational agents or prior administration of succinylcholine enhance the intensity of blockade and duration of Pavulon (see DRUG INTERACTION), these factors should be taken into consideration in selection of initial and incremental dosage.

In adults the initial intravenous dosage range is 0.04 to 0.1 mg. per kg. Later incremental doses starting at 0.01 mg. per kg. may be used. These increments slightly increase the magnitude of the blockade, and significantly increase the duration of blockade, because a significant number of myoneural junctions are still blocked when there is clinical need for more drug.

If Pavulon is used to provide skeletal muscle relaxation for endotracheal intubation, doses of 0.06 to 0.1 mg. per kg. are recommended. Conditions satisfactory for intubation are usually present within 2 to 3 minutes. The ability of the anesthetist to intubate with Pavulon improves with experience.

Dosage in Children: Dose response studies in children indicate that, with the exception of neonates, dosage requirements are the same as for adults. Neonates are especially sensitive to non-depolarizing neuromuscular blocking agents, such as Pavulon, (pancuronium bromide) during the first month of life. It is recommended that a test dose of 0.02 mg. per kg. be given first in this group to measure responsiveness.

Cesarean Section: The dosage to provide relaxation for intubation and operation is the same as for general surgical procedures. The dosage to provide relaxation, following usage of succinylcholine for intubation (see DRUG INTERACTION), is the same as for general surgical procedures.

MANAGEMENT OF PROLONGED NEUROMUSCULAR BLOCKADE: Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Pavulon as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade. Under such circumstances the primary treatment is manual or mechanical ventilation and maintenance of a patent airway until complete recovery of normal respiration is assured. Regonol (pyridostigmine bromide) or neostigmine, in conjunction with atropine, will usually antagonize the skeletal muscle relaxant action of Pavulon. These should be accompanied by or preceded by injection of atropine sulfate to minimize the incidence of cholinergic side effects, notably excessive secretions and bradycardia. Satisfactory reversal can be judged by adequacy of skeletal muscle tone, and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and adjuncts which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade; ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference to the specific package insert of the reversal agents should be made.

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED:

2 ml. ampuls — 2 mg./ml. — boxes of 25, NDC #0052-0444-26
5 ml. ampuls — 2 mg./ml. — boxes of 25, NDC #0052-0444-25
10 ml. vials — 1 mg./ml. — boxes of 25, NDC #0052-0443-25

Organon

Organon Pharmaceuticals
A Division of Organon Inc.
West Orange, N.J. 07052

NARKOMED

TOTAL ANESTHESIA SYSTEM

NARKOMED, a refreshing new concept in anesthesia machine design and styling, incorporating a contemporary anesthesia dispensing system with a built-in fluidic anesthesia ventilator and the widest variety of options.

Please return the accompanying coupon for further information.

NORTH AMERICAN DRÄGER

P.O. BOX 121, TELFORD, PENNSYLVANIA 18969

NORTH AMERICAN DRÄGER

P.O. Box 121
Telford, Pa. 18969

____ Please send information on the NARKOMED TOTAL ANESTHESIA SYSTEM
____ Please include a copy of Anesthesia Accessories Catalog
____ Please send information on _____

NAME _____

TITLE _____

HOSPITAL _____

ADDRESS _____

STATE _____ ZIP _____

ANTILIRIUM
(Physostigmine Salicylate)

REVERSES MOST POST-OPERATIVE DELIRIUM AND PROLONGED SOMNOLENCE

Before prescribing, please consult complete product information, a summary of which follows:

ACTION: ANTILIRIUM (physostigmine salicylate) is a salicylic acid derivative of an alkaloid extracted from seeds of Physostigma Venenosum (calabar bean). The action of the parasympathetic nerves is intermediated by the formation of acetylcholine at the peripheral end of these nerves. Physostigmine inhibits the destructive action of cholinesterase and thereby prolongs and exaggerates the effect of the acetylcholine.

Physostigmine contains a tertiary amine and easily crosses the blood brain barrier, while neostigmine contains a quaternary amine and is not capable of crossing the structure. This may explain why neostigmine does not cause reversal of anticholinergic-induced delirium while physostigmine does.

INDICATIONS: TO REVERSE THE TOXIC EFFECTS UPON THE CENTRAL NERVOUS SYSTEM CAUSED BY DRUGS IN CLINICAL OR TOXIC DOSAGES CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING.

SEVERE ANTICHOLINERGIC POISONING MAY PRODUCE: COMA, MEDULLARY PARALYSIS AND DEATH.

CENTRAL TOXIC EFFECTS MAY INCLUDE: HALLUCINATIONS, DELIRIUM, DISORIENTATION, ANXIETY AND HYPERACTIVITY.

Dramatic reversal within minutes of coma, hallucinations, and other signs can be expected if the diagnosis is correct and the patient has not suffered anoxia or other insult. Therapeutic doses may be necessary at intervals as life-threatening signs recur. Physostigmine is destroyed in the body in 60 to 120 minutes.

CONTRAINDICATIONS: Physostigmine should not be used in the presence of asthma, gangrene, diabetes, cardiovascular disease, mechanical obstruction of the intestines or urogenital tract or any vagotonic state, and in patients receiving choline esters or depolarizing neuromuscular blocking agents.

WARNING: If excessive symptoms of salivation, emesis, urination and defecation occur, the use of ANTILIRIUM should be terminated. If excessive sweating or nausea occur, the dosage should be reduced.

Intravenous administration should be at a slow, controlled rate, no more than 1 mg. per minute (see dosage). Rapid administration can cause bradycardia, hypersalivation leading to respiratory difficulties and possibly convulsions.

An overdosage of ANTILIRIUM can cause a cholinergic crisis.

PRECAUTIONS: Because of the possibility of hypersensitivity in an occasional patient, atropine sulfate injection should always be at hand since it is an antagonist and antidote for physostigmine.

ADMINISTRATION AND DOSAGE: The usual adult dose of ANTILIRIUM is 0.5 to 2.0 mg. intramuscularly or intravenously. Intravenous administration should be at a slow, controlled rate of no more than 1 mg. per minute. It may be necessary to repeat dosages of 1 mg. to 4 mg. at intervals as life threatening signs such as arrhythmias, convulsions and deep coma recur.

IN ALL CASES OF POISONING, THE USUAL SUPPORTIVE MEASURES SHOULD BE UNDERTAKEN.

SUPPLIED: 2 ml. ampules containing: PHYSOSTIGMINE SALICYLATE 1 mg. per ml. Packed 12 ampules per box.

NDC 0456-1037-12

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES:

Greene, L. T.: Physostigmine treatment of anticholinergic drug depression in postoperative patients. Anesth & Analg, March-April 1971; 50-2: 222-226.

Rumack, B.: Anticholinergic poisoning: Treatment with physostigmine. Pediatrics, Sept. 1973.

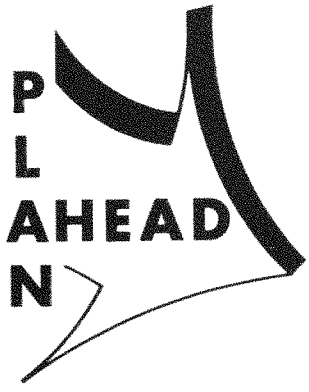
Slovis, T. L., Ott, J. E., Tietelbaum, D. T., and Lipscomb, W.: Physostigmine therapy in acute tricyclic antidepressant poisoning. Clinical Toxicology, 4:451, 1971.

DRUGS AND CHEMICALS CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING:

- AMITRIPTYLINE (Elavil, Triavil, Etrafon)
- ANISOTROPINE METHYLBROMIDE
- ATROPINE
- BELLADONNA
- BENACTYZINE
- CHLORPHENIRAMINE
- CYCLOPENTOLATE
- DESIPRAMINE (Norpramin, Pertofrane)
- DICYCLOMINE
- DIPHENHYDRAMINE
- DOXEPIN (Sinequan)
- HOMATROPINE
- HYOSCINE
- HYOSCYAMUS
- IMIPRAMINE (Tofranil, Presamine)
- ISOPROPAMIDE
- MEPENZOLATE
- METHANTHELINE
- METHAPYRILENE
- NORTRIPTYLINE (Aventyl)
- PIPENZOLATE BROMIDE (Piptal)
- PROPANTHELINE
- PROTRIPTYLINE (Vivactil)
- PYRILAMINE
- SCOPOLAMINE
- STRAMONIUM
- PHENOTHIAZINES
- TRICYCLIC ANTIDEPRESSANTS (Aventyl, Elavil, Etrafon, Norpramin, Pertofrane, Presamine, Tofranil, Triavil, Vivactil)
- THIORIDAZINE (Mellaril)

O'NEAL, JONES & FELDMAN, INC.

2510 METRO BLVD. • ST. LOUIS, MO. 63043 • (314) 569-3610



51ST CONGRESS

MARCH 6-10, 1977

International Anesthesia Research Society

DIPLOMAT RESORT AND COUNTRY CLUBS
HOLLYWOOD, FLORIDA

IMPORTANT INFORMATION ON THE 51st CONGRESS

Pre-registration Material, Program, Hotel Card—will be mailed in mid-December to all I.A.R.S. members, associate members, and educational members. (Members outside of U.S., Canada and Mexico who plan to attend, please advise I.A.R.S. Cleveland office by December 1 to assure timely arrival of pre-registration material.)

Scientific Exhibits—Application forms are available from B. B. Sankey, M.D., Executive Secretary, I.A.R.S., 3645 Warrensville Center Rd., Cleveland, Ohio 44122. There is no deadline for applications; however, applications received after November 1, 1976, are subject to exhibit space availability.

Technical (Commercial) Exhibits—Applications available from Charles B. Slack, Inc., Exhibit Manager, 6900 Grove Rd., Thorofare, New Jersey 08086.

C.M.E. Credit—This Continuing Medical Education offering meets the criteria for Category 1 credit (22 hours est.) for the Physician's Recognition Award of the American Medical Association.

The Board of Trustees

of the

International Anesthesia Research Society

is pleased to announce the appointment of

Dr. Nicholas M. Greene

as Editor-in-Chief

of

Anesthesia and Analgesia . . . Current Researches

effective March, 1977

Dr. Greene succeeds Dr. T. H. Seldon

who is retiring

after 23 years as Editor of the Journal.

Kenneth K. Keown, M.D.

Chairman, Board of Trustees

Arterial and Venous Plasma Levels of Bupivacaine Following Peripheral Nerve Blocks

DANIEL C. MOORE, MD*
LAURENCE E. MATHER, PhD†
L. DONALD BRIDENBAUGH, MD‡
ROBERT I. BALFOUR, MD§
DONALD F. LYSONS, MD‖
WILLIAM G. HORTON, MD**
Seattle, Washington††

Mean arterial plasma (MAP) and peripheral mean venous plasma (MVP) levels of bupivacaine were ascertained in 3 groups of 10 patients each for: (1) intercostal nerve block, 400 mg; (2) block of the sciatic, femoral, and lateral femoral cutaneous nerves, with or without block of the obturator nerve, 400 mg; and (3) supraclavicular brachial plexus block, 300 mg. MAP levels were consistently higher than simultaneously sampled MVP levels, the highest levels occurring from bilateral intercostal nerve block. No evidence of systemic toxicity was observed. The results suggest that bupivacaine has a much wider margin of safety in humans than is now stated.

BUPIVACAINE, like all local anesthetic agents, is used in varying concentrations and volumes, depending on the peripheral nerve-block technic to be employed and on the type of procedure for which it is being performed—surgery, obstetrics, diagnosis, or therapy. If there is no need for rapid establishment of sensory anesthesia, and if complete motor blockade is not required or desired, as for diagnostic or therapeutic peripheral nerve block, 0.25 percent bupivacaine can be employed.[1,2] However, to assure rapid onset of sensory anesthesia and complete motor blockade for surgical procedures after peripheral nerve block, 0.5 percent bupivacaine is required.[1,2]

The purpose of this paper is to report plasma levels of bupivacaine following the use of concentrations, volumes, and milligram doses adequate for all peripheral nerve-block technics.

METHOD OF STUDY

Blocks Studied and Selection of Patients.—Mean arterial plasma (MAP) and mean venous plasma (MVP) levels of bupivacaine were ascertained following: (1) supraclavicular brachial plexus block, in 10 patients; (2) bilateral intercostal nerve block, in 10 patients; and (3) sciatic, femoral, and lateral femoral cutaneous nerve blocks, with or

*Senior Consultant.
†Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington.
‡Staff Anesthesiologist.
§Staff Anesthesiologist.
‖Staff Anesthesiologist.
**Staff Anesthesiologist.
††Department of Anesthesiology, The Mason Clinic, Seattle, Washington 98101.

Read at the 50th Congress of the International Anesthesia Research Society, March 14-18, 1976, Phoenix, Arizona.
Paper received: 4/12/76
Accepted for publication: 5/18/76

LIBRARY

without obturator nerve block, in 10 patients. Patients were not screened but were chosen consecutively, depending on the operating room schedule and the number of patients that could be studied on any specific day. Written informed consent, as approved by the Human Rights Committee of the Virginia Mason Research Center, was obtained from every patient for: (1) block technic; (2) arterial and venous sampling; and (3) bupivacaine dosage.

Premedication.—Premedication was the choice of the resident involved. Patients who had supraclavicular brachial plexus blocks, as well as those given sciatic, femoral, and lateral femoral cutaneous nerve blocks, with or without obturator nerve block, received no sedation other than the premedication, until the surgical procedure began. The 10 patients given bilateral intercostal nerve blocks received 100 to 150 mg of 0.2 percent methohexital solution IV before and during block administration, in addition to the premedication, so that they would not remember being blocked. Methohexital administration was stopped before completion of the block, so patients were able to respond to questions within 10 minutes after block completion.

Dosage of Bupivacaine and Block Technic.—For supraclavicular brachial plexus block, 60 ml of 0.5 percent bupivacaine (300 mg) with 0.25 mg of epinephrine (1:240,000) was injected. For the bilateral block of the 6th through the 12th intercostal nerves, 80 ml of 0.5 percent bupivacaine (400 mg) with 0.25 mg of epinephrine (1:320,000) was administered—5 ml to each of the 14 nerves, or a total of 70 ml plus 10 ml for skin wheals and infiltration. Because we wanted to complete the intercostal nerve blocks in less than 5 minutes, 2 anesthesiologists worked simultaneously (1 on each side). For sciatic, femoral, and lateral femoral cutaneous nerve blocks, with or without obturator nerve block, 80 ml of 0.5 percent bupivacaine (400 mg) with 0.25 mg of epinephrine (1:320,000) was employed. For sciatic nerve block 30 ml was used and the remainder equally distributed among the other nerves to be blocked. Technics were as previously described.[3]

Blood Sampling and Plasma Analysis.—For arterial sampling, a 20-gauge, 3.8-cm Teflon catheter needle was inserted percutaneously into the radial artery. For venous sampling, a 16-gauge, 6.4-cm Teflon catheter needle was inserted in the largest available vein in the cubital fossa of the same arm. IV anesthetics were administered through a 16-gauge, 6.4-cm Teflon catheter inserted in a vein in the opposite hand.

The blocks were performed in a central induction room where the patient remained for at least 30 minutes after completion of the block. In no case was the surgical procedure begun until after the 45-minute sample was drawn. Blood samples were drawn simultaneously from the artery and vein at 0 (control), and then at 5, 10, 15, 20, 25, 30, 45, 60, and 120 minutes from the start of the block by raising of the skin wheal. Plasma levels of bupivacaine were determined by gas chromatography.[4]

Time Determinations.—Elapsed time was calculated to the closest minute. All timing, including sampling times, was determined by stopwatches.

Analysis of Data.—All data were analyzed by the Conversational Computer Statistical System and significance was determined by the test of bivariant correlations.[5]

RESULTS

All 30 blocks produced satisfactory surgical anesthesia, indicating that the solutions of bupivacaine had been placed correctly and in adequate volume and concentration.

Supraclavicular Brachial Plexus Blocks With 60 ml of 0.5 Percent Bupivacaine (300 mg) Containing Epinephrine 1:240,000.—Six of these blocks were completed within 5 minutes, 2 within 7 minutes, and 2 within 8 minutes, with a mean time of 5.5 (SD ± 1.8) minutes for the 10 blocks.

The mean peak arterial and venous plasma levels in 6 men and 4 women, 20 to 69 years of age, weighing 53 kg or more, and undergoing upper extremity surgery, were 1.71 (range 1.05 to 2.40) mcg/ml and 1.55 (range 0.94 to 2.25) mcg/ml, respectively.* They occurred 30 to 35 minutes after injection of the agent (fig 1).

Bilateral Intercostal Nerve Blocks With 80 ml of 0.5 Percent Bupivacaine (400 mg) Containing Epinephrine 1:320,000.—Nine of these blocks were completed within 5 minutes and 1 in 7 minutes, with a mean time of 4.4 (SD ± 0.97) minutes.

*Mean peak level is the highest microgram level attained in plasma from each of the 10 patients in each group.

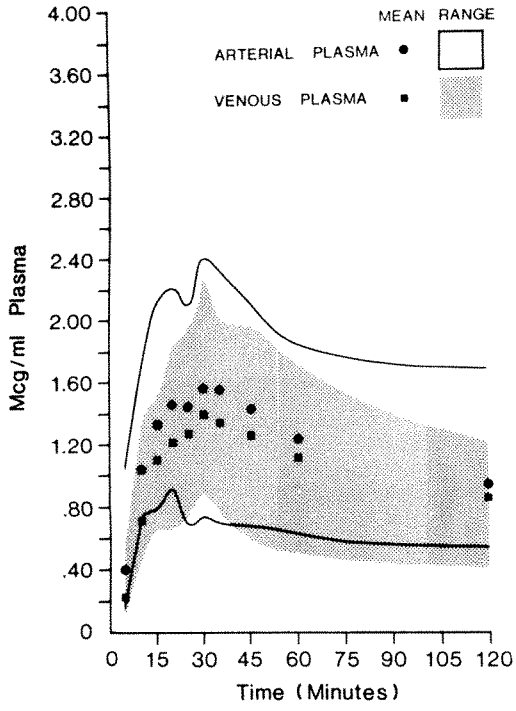


FIG 1. Means and range of arterial and venous plasma levels of 60 ml of bupivacaine 0.5 percent (300 mg) with 1:240,000 epinephrine following supraclavicular block at time intervals of sampling. ● = mean arterial plasma level; black lines = ranges (high and low) of arterial plasma levels; ■ = mean venous plasma level; edges of shaded area = high and low of venous plasma levels.

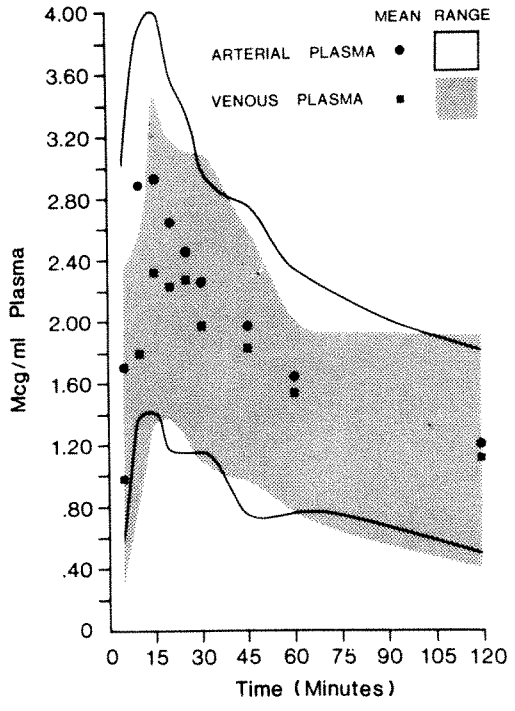


FIG 2. Means and range of arterial and venous plasma levels of 80 ml of bupivacaine 0.5 percent (400 mg) with 1:320,000 epinephrine following bilateral intercostal nerve block at the time intervals of sampling. ● = mean arterial plasma level; black lines = ranges (high and low) of arterial plasma levels; ■ = mean venous plasma level; edges of shaded area = high and low of venous plasma levels.

The mean peak arterial and venous plasma levels in 6 men and 4 women, 20 to 72 years of age, weighing 49 kg or more, undergoing upper intraabdominal surgery, were 3.29 (range 1.72 to 4) mcg/ml and 2.52 (range 1.4 to 3.45) mcg/ml, respectively. They occurred 10 to 20 minutes after injection of the agent (fig 2).

Sciatic, Femoral, and Lateral Femoral Cutaneous Nerve Block With or Without Obturator Nerve Block With 80 ml of 0.5 Percent Bupivacaine (400 mg) Containing Epinephrine 1:320,000.—Two of these blocks were completed within 7 minutes, 5 within 8 minutes, 2 within 10 minutes, and 1 within 14 minutes, with a mean time for the 10 patients of 8.8 (± 2.1) minutes.

The mean peak arterial and venous plasma levels in 6 male and 4 female patients, 14 to 79 years of age, 1 weighing 39 kg and the others 60 kg or more, for lower extremity surgery, were 1.89 (range 1.0 to 3.16) mcg/ml and 1.6 (range 0.84 to 2.73) mcg/ml, respectively. They occurred within 15 minutes after injection of the agent, these levels persisting for up to 60 minutes (fig 3).

DISCUSSION

Selection of Blocks Studied and Dosages of Bupivacaine and Epinephrine.—Peripheral nerve blocks were investigated in this study because: (1) we frequently employ them, particularly in the patient with poor physical status—ASA status III, IV, or V; (2) they may sometimes require a higher volume (60 to 80 ml) of 0.5 percent bupivacaine for rapid establishment of surgical sensory anesthesia and for complete motor blockade; and (3) if systemic toxic reactions are to occur from bupivacaine *absorption* in any block technic, this would most likely be after such blocks.[6] In addition, bilateral intercostal nerve block can usually be completed within a 5-minute period; when it is done rapidly and properly, the plasma levels of local anesthetic agents peak sooner and are higher than with any other regional nerve block studied to date.[7,8]

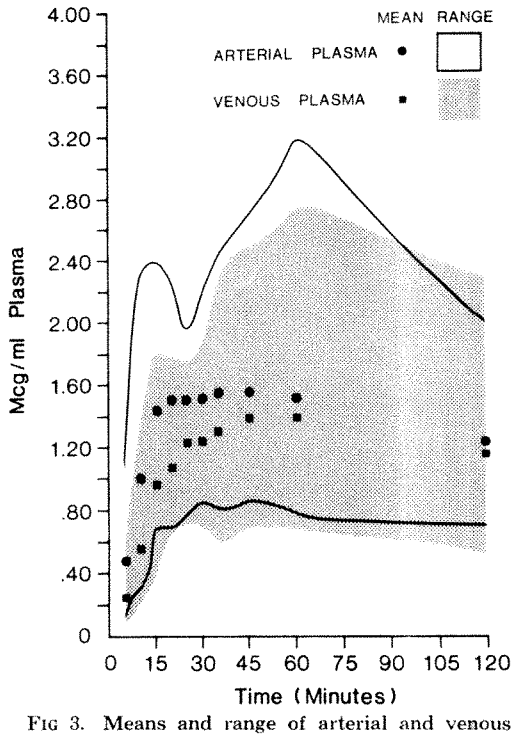


FIG 3. Means and range of arterial and venous plasma levels of 80 ml of bupivacaine 0.5 percent (400 mg) with 1:320,000 epinephrine following sciatic, femoral, and lateral femoral cutaneous nerve blocks with or without obturator nerve block at time intervals of sampling. • = mean arterial plasma level; black lines = ranges (high and low) of arterial plasma levels; ■ = mean venous plasma level; edges of shaded area = high and low of venous plasma levels.

The volumes and concentrations for these blocks were chosen because they are the approximate maxima that might be required to result in effective sensory and motor blockade under any circumstance, clinical or teaching. If a volume greater than 80 ml is required—for example, 100 ml for a bilateral intercostal nerve block with celiac plexus block—the necessary volume may be obtained by adding 20 ml of normal saline solution to the 80 ml of 0.5 percent (400 mg) of the bupivacaine solution. This would lower rather than raise plasma levels of bupivacaine because the weaker the concentration, the lower the plasma level of the local anesthetic.[8] Furthermore, the slight reduction in the concentrations of the bupivacaine solutions will not noticeably affect sensory or motor anesthesia.

All solutions in this study contained epinephrine. Epinephrine is added to most local anesthetic solutions because it lowers the blood level of such agents by slowing absorption from the site of injection.[3,9] We seldom exceed a dose of 0.25 mg of epinephrine regardless of volume of the local anesthetic solution injected.[3] Therefore, the solutions used contained epinephrine 1:240,000 (0.25 mg/60 ml) and 1:320,000 (0.25 mg/80 ml), which are considered less than the optimal [1:200,000 (0.1 mg/20 ml)].[3,9-11]

Arterial and Venous Plasma Levels.—Plasma levels were selected rather than whole blood because plasma is easier to analyze and 95 percent of bupivacaine is protein-bound in the plasma.[12]

Arterial levels were compared with peripheral venous levels because they more closely reflect changes in drug levels in well-perfused vital organs and are more sensitive to change in drug absorption and disposition.[13] Venous sampling is more subject to variability and artifact due to local circulatory changes in the sampling site, in which case the resultant blood concentration profile may lead to erroneous conclusions.[14] For these reasons, toxic effects may be more reliably associated with arterial rather than venous levels.*[14]

Following bilateral intercostal nerve block, MAP levels were 20 to 25 percent higher than simultaneously sampled venous plasma levels. They occurred earlier and the arteriovenous differences persisted for approximately 60 minutes after injection (fig 2). Such marked differences did not occur in the arteriovenous plasma levels of the other 2 block technics studied, in which plasma levels peaked later and were significantly lower than those occurring after bilateral intercostal nerve block (fig 1 and 3). In part, this is due to: (1) the lower dose used in brachial plexus block; (2) the longer time needed to execute brachial plexus and sciatic, femoral, and lateral femoral cutaneous nerve blocks; and (3) circulatory differences of the areas.

Systemic Toxicity.—Plasma levels of bupivacaine resulting in convulsions in man have been reported as 4 mcg/ml or higher.[13] In only 1 of our 30 patients did the arterial plasma level peak at 4 mcg/ml in 15 minutes following a bilateral intercostal nerve block. No systemic toxic reactions were observed in any of the 30 patients. We did not expect any such reactions; from 1966 through 1975, we administered 0.25 or 0.5 percent bupivacaine for 3137 peripheral nerve blocks, with and without epinephrine, with no evidence of systemic toxicity. Of these, 2520

*Tucker GT, Mather LE: Personal communication.

TABLE
Bupivacaine (mg) Used for Single-Dose Blocks Reported Herein 1966-1975

Milligram dosage	Number of patients			
	Brachial plexus	Sciatic, femoral, etc.	Inter-costal	Total
150 or less	238	74	345	657
151-200	57	78	261	396
201-250	95	218	318	631
251-300	109	63	438	610
301-350	5	44	24	73
351-400	9	15	72	96
401-450	5	7	36	48
451-600		2	7	9
	518	501	1501	2520

were the same blocks investigated in this study (table).

Such factors as age, weight, and underlying disease have been said to influence the development of systemic toxic reactions.[3,9,10] The degree of importance of these factors in adults, if any, needs verification. No correlations between these factors and maximum plasma levels were found in our previous study of bupivacaine or of mepivacaine, whose chemical structure closely resembles that of bupivacaine (bupivacaine contains a butyl radical where mepivacaine contains a methyl radical[8,15]). Likewise, in the small patient population reported herein, the bivariant correlations between predictor variables (sex, age, height, weight, and physical status) and each of the various plasma-level criteria were of no significance.

In the sciatic, femoral, and lateral femoral cutaneous nerve block group of 10 patients, the 79-year-old woman weighed 39 kg, was 157 cm tall, with a physical status of ASA II. Her block took 7 minutes to execute, and peak arterial and venous levels were 2.38 mcg/ml and 1.80 mcg/ml, respectively, in 15 minutes. These levels were not the highest in the ranges and may further indicate that age and weight are of little significance in determining dosage.

The principal factor in determining nontoxic dosage in adults is probably the specific regional block technic, considering (1) the area of the body injected; (2) its vascularity; and (3) the possibility of an intravascular injection from a needle whose position is not changed during injection of a large dose of the local anesthetic agent, as in epidural (peridural) block. In our peripheral nerve blocks, it is unlikely that a large bolus would be injected intravascularly, for the position of the needle is seldom fixed in a single position during the entire block procedure.[3]

Although premedication may mask, ameliorate, or prevent systemic toxic reaction, it is doubtful that this occurred in our 30 patients. Nineteen received meperidine (50 to 125 mg), while 11 received morphine (8 to 15 mg). Eight patients received no other premedication. The remaining patients received along with the IM narcotic: (1) atropine 0.4 mg (n = 15); (2) scopolamine 0.4 mg (n = 2); (3) diazepam 10 mg (n = 4); or (4) atropine 0.4 mg with hydroxyzine 75 mg (n = 1).* Perhaps the methohexital administered during bilateral intercostal nerve block could have prevented recognition of a systemic toxic reaction, but this is doubtful because the dose was minimal.

Shivering.—Shivering has been cited as possible evidence of a mild systemic toxic reaction after bupivacaine administration.[1,2,16] Therefore, this sign was carefully observed, both in the induction room, where all blocks were performed and the temperatures were 23.3° C or above, and in the operating rooms, where the temperatures were 21.1° C or less. In the induction room, where the patient remained for at least 30 minutes after block completion, none of the patients shivered. In the operating rooms, shivering occurred in 3 of the 10 patients given bilateral intercostal nerve blocks, but in none of the patients in whom the extremity was blocked. In a previous study of parturients, shivering was higher with 0.25 percent than with 0.5 percent solutions of bupivacaine.[16] In both instances, shivering occurred when temperatures in the rooms were between 18.3 and 21.1° C. Shivering may result from a number of variables such as room temperature or degree of block of the sympathetic nervous system, the least influential of which may be the local anesthetic agent.

Systemic Toxicity and Package Inserts.—In countries other than the USA, the dosage of 0.25 and 0.5 percent concentrations of bupivacaine is 2 mg/kg, with the maximum of 100 mg without epinephrine and 150 mg

*n = number of patients.

with epinephrine 1:200,000.* In the USA, maximum doses of such concentrations have not been determined, and the package insert states: (a) "Most experience to date is with single doses of Marcaine up to 225 mg with epinephrine 1:200,000, and 175 mg without epinephrine; more or less drug may be used depending on the individualization of each case;" and (b) "In clinical studies to date, total daily doses have been up to 400 mg. Until further experience is gained, this dose should not be exceeded in 24 hours."† However, some physicians misinterpret point (a) to mean that these doses stated represent maximum total dosage.

From our clinical experiences with bupivacaine and peripheral nerve block from 1966 through March 1975, involving 3137 patients, of whom 1863 received in excess of 150 mg and at least 836 in excess of 225 mg (table), as well as from the plasma studies reported herein, such restrictions appear unnecessarily stringent and in need of revision because bupivacaine apparently has a much greater margin of safety in humans than the package insert indicates, and dosages as stated in the inserts of other countries markedly limit the use of this versatile, long-acting local anesthetic agent in single-dose peripheral nerve blocks.

A Word of Caution.—Readers are cautioned that the 0.75 percent solution of bupivacaine available in the USA was developed for use in single-dose epidural or caudal block *only*—not for peripheral nerve-block technics.[1,2] If this concentration is used for peripheral nerve block in the dosages described above, systemic toxic reactions might occur, because the higher the concentration of a local anesthetic in the same milligram dose, the higher the blood level of the agent.[8]

ACKNOWLEDGMENT

The authors thank Gayle DeBay for determination of plasma levels in the gas chromatograph laboratory at the University of Washington School of Medicine, Department of Anesthesiology, under the directorship of Laurence E. Mather, Ph.D. Also for programming and analysis of data appreciation is expressed to Jeri Kronmal and James Hayes, Ph.D.

*As stated in package inserts from Australia, Brazil, England, France, Germany, Japan, Netherlands, and New Zealand; British Pharmaceutical Codex, Pharmaceutical Press of London, 1973; and Martindale: The Extra Pharmacopoeia, 26th edition, Pharmaceutical Press of London, 1967. Copies supplied on request.

†Package insert of Winthrop Laboratories (revised October 1974), New York, New York.

REFERENCES

1. Moore DC, Bridenbaugh LD, Bridenbaugh PO, et al: Bupivacaine, a review of 2077 cases. JAMA 214:713-718, 1970

2. Moore DC, Bridenbaugh LD, Bridenbaugh PO, et al: Bupivacaine hydrochloride: a summary of investigational use in 3274 cases. Anesth Analg 50:856-872, 1971

3. Moore DC: Regional Block. Fourth edition (sixth printing). Springfield, Illinois, Charles C Thomas, Publisher, 1975

4. Mather LE, Tucker GT: Meperidine and other basic drugs: general method for their determination in plasma. J Pharm Sci 63:306-307, 1974

5. Kronmal RA, Bender L, Mortensen J: Conversational computer statistical system for medical records. J Roy Stat Soc 19:82-92, 1970

6. New classification of physical status. Anesthesiology 24:111, 1963

7. Braid DP, Scott DB: The sytemic absorption of local analgesic drugs. Br J Anaesth 37:394-404, 1965

8. Tucker GT, Moore DC, Bridenbaugh PO, et al: Systemic absorption of mepivacaine in commonly used regional block procedures. Anesthesiology 37: 277-287, 1972

9. Bonica JJ: Management of Pain. Philadelphia, Lea & Febiger, 1953

10. Moore DC: Complications of Regional Anesthesia. Springfield, Illinois, Charles C Thomas, Publisher, 1955

11. Braun H: Local Anesthesia. Third edition. Philadelphia, Lea & Febiger, 1914

12. Tucker GT, Boyes RN, Bridenbaugh PO, et al: Binding of anilide-type local anesthetic in human plasma: I. Relationships between binding, physiochemical properties, and anesthetic activity. Anesthesiology 33:287-303, 1970

13. Jorfeldt L, Löfstrom B, Pernow B, et al: The effect of local anaesthetics on the central circulation and respiration in man and dog. Acta Anaesthesiol Scand 12:153-169, 1968

14. Tucker GT, Mather LE: Pharmacokinetics of local anaesthetic agents. Br J Anaesth 47:213-224, 1975

15. Moore DC, Mather LE, Bridenbaugh PO, et al: Arterial and venous plasma levels of bupivacaine following epidural and intercostal nerve blocks. Anesthesiology 45:39-45, 1976

16. Moore DC, Bridenbaugh PO, Bridenbaugh LD, et al: Bupivacaine compared with etidocaine for vaginal delivery. Anesth Analg 54:250-256, 1975

Advantages of Infant Ventilators Over Adapted Adult Ventilators in Pediatrics

ROBERT E. BINDA, JR, MD*
DAVID R. COOK, MD†
CARL G. FISCHER, MD‡
Pittsburgh, Pennsylvania§

A lung simulator with variable compliance and resistance components was used to evaluate the dynamic compliance of the Bournes, Babybird, and Pediatric Emerson postoperative ventilators. With increase in airway pressure from combined changes in compliance and resistance, the internal compliance of the Bournes was lowest and the internal compliance of the Emerson was highest. With low constant airway resistance (50 cm/L/sec), the Babybird exhibited tidal volume losses similar to those of the Bournes in the face of decreased lung compliance. With constant lung compliance (10 ml/cm H_2O) and increasing airway resistance, the Babybird had marked volume losses at higher volumes. Under all simulated conditions, internal compliance of the Emerson, although large, was relatively constant and the Bournes had the smallest internal compliance.

WHEN mechanical ventilators are used for infants and small children, significant volumes of gas may be lost to the patient as airway pressure increases as a result of (1) compression of gas in the internal volume of the ventilator and (2) distention of the flexible tubing that connects ventilator and patient. As airway pressure rises from either a decrease in lung compliance or an increase in airway resistance, there will be a decrease in delivered volume. These volume losses may have significant effects on the minute volume and hence gas exchange in infants.[1]

We compared the volume losses from increased airway pressure in an adult ventilator adapted for pediatric use and in 2 ventilators specificially designed for infants. In addition, we evaluated the difference between volume losses when the increase in airway pressure was first produced by a decrease in compliance and second by an increase in airway resistance.

MATERIAL AND METHODS

Three infant ventilators were compared: the Emerson postoperative with pediatric piston and modified for IMV, a Babybird, and a Bournes. These were selected at random from those used daily in the intensive care unit, and each was studied with a full humidifier in place.[2] All were equipped with Tygon patient tubing.

Ventilator function was tested with a Bournes Infant Lung Simulator, which consists of several 150-ml containers of known

*Assistant Professor of Anesthesiology.
†Assistant Professor of Anesthesiology.
‡Assistant Professor of Anesthesiology.
§Department of Anesthesiology, University of Pittsburgh School of Medicine and Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania 15213.

Paper received: 11/10/75
Accepted for publication: 3/15/76

compliance, connected in series by nondistensible Tygon tubing. The containers are filled with finely divided copper wool to ensure that compression of gas within them is isothermal and not adiabatic.[3] Compliance can be varied from 10 to 1 ml/cm H_2O. The simulator also allows changes in airway resistance from 50 to 500 cm H_2O/L/sec by interchanging small metal filters proximal to the compliance component. In all studies, a 3.5-mm OD endotracheal tube was interposed between the ventilator and the lung simulator.[4] Air was used as the gas in all studies.

Peak airway pressure and lung pressure were measured with aneroid manometers connected to the simulator. These pressures were secondarily displayed on an oscilloscope that could be marked for calibration. By knowing the compliance and lung pressure, the simulator could be used as a "pneumatic integrator," the delivered lung volume being the product of compliance (ml/cm H_2O) and lung pressure (cm H_2O).

To test the accuracy of this pneumatic integrator, a 3.5-mm OD endotracheal tube was connected to a Fleisch #0 pneumotachograph. The pressure drop across the resistance of the pneumotachograph was measured by a differential pressure transducer, amplified, integrated, and gas flow and volume recorded on a Grass polychannel recorder. A Hamilton syringe and an oiled glass syringe were used to calibrate the electronic integrator on the Grass recorder for volume. There was linear response in the electronic integrator from 20 to 200 ml tidal volume.

The pneumotachograph head was then interposed between the resistance component and one of the compliance containers. Volume from a piston ventilator was delivered to the lung simulator and resistance varied from 50 to 500 cm H_2O/L/sec. The delivered volumes to the lung calculated from the pneumatic integrator of the Bournes simulator and from the electronic integrator agreed within ± 5 percent. The calculated internal compliance of the ventilator using the two differently derived volumes was essentially the same.

The internal compliance of a ventilator is a measure of the volume lost within a ventilator system following rises in airway pressure during gas flow. The higher the internal compliance of a ventilator system, the greater the amount of gas it can accommodate without transferring this volume to the patient in response to an increase in pressure within the ventilator.

The experiment was divided into 3 parts. In each part, the ventilators were adjusted to provide ± 100, 60, and 40 ml delivered lung volume at the lowest resistance and highest compliance on the lung simulator at a ventilator rate of 20/min.

In part A, compliance was decreased in steps and resistance was increased to give 12 progressive increases in airway pressure. The 12 compliances of the lung and lung pressures were noted at each setting. The delivered volume was then calculated.

In part B, airway resistance was kept constant while compliance was decreased in 4 steps from 10 to 1 ml/cm H_2O, and again delivered volume was calculated.

In part C, compliance was maintained constant at 10 ml/cm H_2O, while airway resistance was increased in 7 steps from 50 to 500 cm/L/sec.

For each volume in all 3 parts, a linear regression equation was derived from the calculated lung volume and airway pressures. The correlation coefficient was calculated. The slope of this regression line is the internal (effective) compliance of the ventilator.

The slope of the calculated regression line is the volume lost/cm H_2O change in pressure. Student's *t*-test was used to determine the significance of slope differences for each ventilator at comparable preset volumes.

RESULTS

In part A of this study, where both airway resistance and lung compliance were varied, the Bournes ventilator had the lowest internal compliance, the Babybird had twice this value, and the Emerson had 5 times this value at the several volumes studied (table 1). The volume losses to the patient as peak airway pressure rises are significantly greater with the Babybird and Emerson than with the Bournes; volume losses with the Emerson were greater than with the Babybird.

When the airway resistance is constant, the Babybird and Bournes have comparable volume losses as airway pressure increases because of decreases in lung compliance (table 2). The Emerson has 4 to 5 times the volume loss of the other two.

TABLE 1
Tidal Volume Losses with Combined Changes in Compliance and Airway Resistance*

	Preset volume, ml	Volume lost, −ml/cm H_2O	r
Bournes	60	1.3†	−0.98
Bournes	40	1.1	−0.97
Babybird	60	2.6‡	−0.94
Babybird	40	2.0	−0.95
Emerson	70	6.4	−0.92
Emerson	50	5.6	−0.91

*Initial lung compliance was set at 10 ml/cm H_2O and airway resistance at 50 cm H_2O/L/sec.

†Different from Babybird and Emerson at both preset volumes ($p<0.001$).

‡Different from Emerson at both preset volumes ($p<0.001$).

TABLE 2
Tidal Volume Losses with Decreasing Lung Compliance and Constant Airway Resistance*

	Preset volume, ml	Volume lost, −ml/cm H_2O	r
Bournes	90	1.2†	−0.97
Bournes	60	1.2	−0.94
Bournes	30	0.8	−0.94
Babybird	100	1.3‡	−0.95
Babybird	60	1.3	−0.95
Babybird	30	0.9	−0.86
Emerson	100	5.7	−0.97
Emerson	60	5.1	−0.98
Emerson	30	5.2	−0.95

*Airway resistance was kept at 50 cm H_2O/L/sec and lung compliance was decreased from 10 ml/cm H_2O to 1 ml/cm H_2O.

†Not significantly different from the Babybird at all preset volumes ($p<0.50$); different from the Emerson at all preset volumes ($p<0.001$).

‡Different from the Emerson and all preset volumes ($p<0.001$).

With constant lung compliance and increasing airway resistance at all tidal volumes, both the Babybird and Emerson had significantly higher volume losses than did the Bournes (table 3). At the 60 and 100 ml tidal volumes, the volume losses from the Babybird and Emerson were of about the same magnitude, although different. At the 30 ml tidal volume, the volume losses from the Babybird were significantly lower than that of the Emerson.

TABLE 3
Tidal Volume Losses with Increasing Airway Resistance and Constant Lung Compliance*

	Preset volume, ml	Volume lost, −ml/cm H_2O	r
Bournes	80	1.6†	−0.99
Bournes	60	1.2	−0.98
Bournes	30	1.2	−0.98
Babybird	100	5.3‡	−0.99
Babybird	60	4.7‡	−0.98
Babybird	30	1.9§	−0.99
Emerson	100	4.0	−0.99
Emerson	60	5.7	−0.99
Emerson	30	6.0	−0.88

*Lung compliance was kept at 10 ml/cm H_2O and airway resistance was increased from 50 cm H_2O/L/sec to 500 cm H_2O/L/sec.

†Different at all volumes from Babybird and Emerson ($p<0.05$).

‡Not different from Emerson ($p<0.10$).

§Babybird different from Emerson ($p<0.05$).

DISCUSSION

A lung simulator allows variation in airway resistance and lung compliance separately, approximating the conditions encountered in a patient with pulmonary disease. Such a device provides a method for comparing the performance of various pediatric ventilators. The Bournes simulator is patterned after the simulator suggested by the International Standards Committee.[5]

When airway resistance was increased and lung compliance decreased, the Bournes ventilator had the lowest internal compliance. Lower internal compliance reflects smaller tidal volume losses with increases in airway pressures. The Babybird had approximately twice and the Emerson had approximately 5 times the internal compliance of the Bournes.

When airway resistance was constant, the Babybird improved its performance to the level of the Bournes. However, when increased airway resistance was simulated, the internal compliance of the Babybird was similar to that of the Emerson. Since the tidal volume of a Babybird is flow-generated, as airway resistance is increased, the delivered flow will decrease.

This relation between flow, pressure, and resistance in the airway is generally analogous to the relationship between current, electromotive force, and resistance in an electric circuit, as expressed in Ohm's Law:

$$\text{Current (i)} = \frac{\text{Electromotive force (E)}}{\text{Resistance (R)}}$$

$$\text{Flow (F)} \propto \frac{\text{Pressure (P)}}{\text{Resistance (R)}}$$

Since delivered tidal volumes flow from areas of high pressure (within the ventilator) to areas of relatively low pressure (within the lung) and since this pressure dfferential remains relatively constant, any increase in airway resistance will result in a decrease in delivered flow.

In the Babybird ventilator, which is time cycled, the tidal volume is the product of the flow rate and the inspiratory time. If the delivered flow is decreased because of an increase in airway resistance, the tidal volume delivered is likewise decreased.

No ventilator functions as a true "volume" ventilator when used to ventilate infants. In part, compression and distention volume losses can be compensated for by increasing the preset tidal volume of the ventilator above the required patient tidal volume. This provides an adequate patient tidal volume when airway pressure remains constant. If airway pressure rises, significant tidal volume losses to the infant may occur; in adults this volume loss due to increased airway pressure represents a small fraction of the patient tidal volume.

One of the factors influencing the compression volume loss is the size of the internal volume of the ventilator,[2] the larger the internal volume, the larger the tidal volume losses. Even though compression volume losses in the Emerson can be anticipated and additional tidal volume used to allow for these losses, subsequent changes in airway pressures will result in greater volume losses in the adult ventilators.

Therefore, there is a definite advantage in using infant ventilators (with small internal volumes) for the mechanical ventilation of infants rather than adapting adult ventilators for this purpose.

REFERENCES

1. Robbins L, Crocker D, Smith RM: Tidal volume losses of volume-limited ventilators. Anesth Analg 46:428-431, 1967

2. Haddad C, Richards C: Mechanical ventilation of infants. Anesthesiology 29:365-370, 1968

3. Hill DW, Moore V: The action of adiabatic effects on the compliance of an artificial thorax. Br J Anaesth 37:19-22, 1965

4. Mattila M: The role of the physical characteristics of the respirator in artificial ventilation of the newborn. Acta Anaesthesiol Scand Suppl 56: 9-107, 1974

5. Keuskamp DH: Ventilation of premature and newborn infants. Int Anesthesiol Clin 12:281-307, 1974

POSTOPERATIVE RENAL FAILURE. Since acute renal failure (ARF) in the postoperative period has an extremely poor prognosis, it is important to be able to predict preoperatively the patients at risk. A prospective study of 500 consecutive cardiac operations evaluated the incidence, etiology and therapy of postoperative ARF. Thirty-five patients developed ARF. Positive risk factors included age, elevated preoperative renal function tests (BUN, serum creatinine, creatinine clearance) reduced cardiac output preoperatively, duration of cardiopulmonary bypass and duration of aortic cross clamping. Factors that did not correlate with the development of ARF included the type of operation, intraoperative blood pressure or urine output, flow rate during cardiopulmonary bypass, hemoglobinemia or preoperative diuretic therapy. Mortality was 88.8 percent and 100 percent if dialysis was required. Postoperative ARF is better prevented than treated. *(Abel RA, Buckley MJ, Austen WG et al: Etiology, incidence and prognosis of renal failure following cardiac operations. Results of a prospective analysis of 500 consecutive patients. J Thor Cardiovas Surg 71:323-333, 1976)*

Ketamine and Intraocular Pressure in Children

BAIBA AUSINSCH, MD*
ROBERT L. RAYBURN, MD†
EDWIN S. MUNSON, MD‡
NORMAN S. LEVY, MD, PhD§
Gainesville, Florida‖

The effect of ketamine on intraocular pressure (IOP) was studied in 10 children. Control IOP values were determined prior to induction of anesthesia, following premedication with atropine alone or in combination with pentobarbital and meperidine. After the IM injection of 8 mg/kg of ketamine, the IOP was determined at 5, 10, 15, and 20 minutes. Mean (± SD) IOP values before and after ketamine were 22.2 ± 4.8 and 16.7 ± 3.3 torr ($p<0.001$), respectively. The authors believe that the reduction in IOP was not due to ketamine, per se, but rather to lack of patient relaxation and cooperation during control measurements. At the end of 20 minutes, a second dose of ketamine, this time 1 mg/kg IV, was given and measurements were repeated at the same intervals. In 5 patients, the effects on IOP of d-tubocurarine, endotracheal intubation, and N_2O inhalation also were evaluated. A significant increase (6.7 torr) in IOP was observed only after endotracheal intubation. The authors conclude that ketamine does not raise IOP in the healthy pediatric patient and, therefore, can be used for ophthalmic procedures requiring sedation or anesthesia.

KNOWLEDGE of the effect of anesthetic agents on intraocular pressure (IOP) is important in the selection of anesthesia for patients with elevated IOP or open eyeball injuries. While most inhalation anesthetics produce little or no decrease in IOP,[1-3] ketamine has been reported to increase IOP markedly[4,5] or to a mild degree.[6,7] Yet another study[8] in adults reported that ketamine had no effect on IOP.

Furthermore, knowledge of the normal range of IOP associated with the use of ketamine is necessary for the ophthalmologist in the diagnosis and treatment of glaucoma. We therefore evaluated the effects of ketamine on IOP in a group of healthy pediatric patients. The effects on IOP of d-tubocurarine, endotracheal intubation, and N_2O inhalation were also examined.

METHODS

Ten healthy children who showed no evidence of intraocular disease were studied. Ages ranged from 2 to 10 (mean 5.7) years and mean weight was 21.5 ± 8.1 kg. Informed consent was obtained from parents or guardians and the experimental protocol was approved by the University's Committee for the Protection of Human Subjects.

*Assistant Professor of Anesthesiology.

†Resident in Anesthesiology and Pediatrics.

‡Professor of Anesthesiology.

§Assistant Professor of Ophthalmology.

‖Departments of Anesthesiology, Pediatrics, and Ophthalmology, University of Florida College of Medicine, J. Hillis Miller Health Center, Gainesville, Florida 32610.

This study was supported in part by the National Institutes of Health General Research Support Grant #RR05362-13 and the National Institutes of Health Research Training Grant #5T01 GM 00427.

Reprint requests to Dr. Munson, Department of Anesthesiology, University of Florida College of Medicine, Box J-254, J. Hillis Miller Health Center, Gainesville, Florida 32610.

Paper received: 1/29/76
Accepted for publication: 3/9/76

Each patient received 0.02 mg/kg of atropine IM 1 hour before the study, 5 also receiving 1.1 mg/kg of meperidine and 2.2 to 4.4 mg/kg of pentobarbital IM. Studies were conducted in a quiet room adjacent to the operating room. Following corneal application of 0.5 percent proparacaine hydrochloride ophthalmic solution, control measurements of IOP were obtained in both eyes with a MacKay-Marg electronic applanation tonometer.[9] Blood pressure was monitored throughout the study period by standard arm-cuff occlusion. The ECG (lead II) recorded cardiac rate and rhythm.

The protocol was divided into two phases. In phase I, anesthesia was induced in all 10 patients with 8 mg/kg of ketamine IM. IOP measurements were made after 5, 10, 15, and 20 minutes while patients spontaneously breathed room air. Phase II began with the administration of a 2nd dose of 1 mg/kg of ketamine IV, 20 minutes after the initial IM dose. Patients were then randomly divided into 2 equal groups.

In group A (controls), IOP measurements were recorded in 5 patients after 5, 10, and 15 minutes while breathing 100 percent O_2. The other 5 patients received 0.8 mg/kg of d-tubocurarine IV in addition to the 2nd dose of ketamine. They were ventilated with O_2, and 5 minutes later IOP was measured. Muscular response was evaluated by ulnar nerve stimulation at the wrist with a Wellcome peripheral nerve stimulator. The tracheas of these patients then were intubated with the aid of a straight laryngoscope blade and, after a period of 5 minutes, IOP measurements were determined. N_2O-O_2 (70:30) was then administered, and IOP was again measured at 5 minutes in 5 patients and at 10 minutes in 3 patients.

The average pressure in both eyes was used in the tabulations and in statistical analysis of paired data by Student's *t*-test.

RESULTS

Phase I: Mean (± SD) IOP values before and after ketamine (8 mg/kg) were 22.2 ± 4.8 and 16.7 ± 3.3 torr ($p<0.001$), respectively (table 1). The reduction in IOP persisted throughout the 20-minute observation period. Although 5 of 10 children received premedication, only 3 were relaxed and cooperative during control IOP measurements. In the 3 children in whom adequate control measurements were obtained, IOP was 17.5 ± 2.6 torr, a value significantly less ($p<0.05$) than for the 7 uncooperative patients (24 ± 3.5).

TABLE 1
IOP Values Before and After Ketamine 8 mg/kg in 10 Children (Phase I) (Mean ± SD)

	IOP (torr) minutes after ketamine			
Control	5	10	15	20
22.2	16.7*	17.2†	17.5†	17.0†
±4.8	±3.3	±3.3	±3.4	±4.2

*$p<0.001$.
†$p<0.02$.

TABLE 2
IOP Values After Ketamine 1 mg/kg in 5 Children (Phase IIA) (Mean ± SD)

	IOP (torr) minutes after ketamine		
Control*	5	10	15
16.2	17.4	15.8	15.4
±3.6	±2.7	±2.1	±2.1

*Represents 20-minute value after previous ketamine (8 mg/kg IM).

TABLE 3
IOP Values After Ketamine (1 mg/kg IV) and Other Drugs in 5 Children (Phase IIB) (Mean ± SD)

	IOP (torr) minutes after ketamine			
	5	10	15	20
Control*	Ketamine and d-tubocurarine†	Endotracheal intubation	Nitrous oxide	Nitrous oxide
17.7	15.5	22.2‡	18.0	15.3§
±5.1	±4.6	±4.1	±2.9	(14 to 17)

*Represents 20-minute value after previous ketamine (8 mg/kg IM).
†0.8 mg/kg IV.
‡$p<0.05$ from all other values.
§Represents mean (and range) in 3 patients.

No IOP differences after ketamine were observed between premedicated and unpremedicated children. Both systolic blood pressure and heart rate showed a significant ($p<0.05$) increase (10 and 16 percent, respectively) 5 minutes after ketamine administration. These changes were maintained throughout the study period.

Phase II: Mean (± SD) IOP values after IV ketamine (1 mg/kg) in 5 children are shown in table 2. No significant effect on IOP was observed when compared to the 20-minute value after the initial IM ketamine. The administration of a paralyzing dose of d-tubocurarine in the other 5 patients resulted in a small (2.2 torr) but insignificant decrease in IOP (table 3). The

greatest change in IOP occurred after endotracheal intubation, when a 6.7 torr increase ($p<0.05$) was observed. A 10 percent increase ($p<0.05$) in systolic blood pressure also occurred at this time. No change in heart rate was observed. Following N_2O administration, IOP and systolic blood pressure returned to control levels.

DISCUSSION

In contrast to the reports of others,[4-7] our findings show that ketamine anesthesia does not produce an increase in IOP. Mean IOP values during 35 minutes of ketamine anesthesia ranged from 15.4 to 17.5 torr, values similar to those we previously reported for halothane and isoflurane.[1] The presence or absence of narcotic-barbiturate premedication did not affect this response. These observations, and the finding that a paralyzing dose of d-tubocurarine failed to produce further lowering of IOP, indicate that an IOP value of 16 to 17 torr (as determined by applanation tonometry) probably represents a basal pressure in the anesthetized state.

When compared to awake control measurements, we observed a small but significant reduction in IOP after ketamine administration. However, we believe that this reduction was not an effect of ketamine, per se, but rather related to the lack of relaxation and patient cooperation in most children during control measurements. Five of our patients received premedication and adequate cooperation was achieved in only 3. In contrast, sedated control IOP measurements in our previous study of a larger group of children[1] showed an IOP value of 17.4 ± 3.4 torr, which is similar to that observed in our 3 cooperative sedated patients before ketamine, and in all 10 patients after ketamine in this study (table 1).

The observation of a significantly elevated IOP 5 minutes after endotracheal intubation was unanticipated and is not readily explained. However, it does suggest that the finding of an elevated IOP immediately after endotracheal intubation should be viewed with caution in a child with an open eye and anesthetized with ketamine. Similarly, this response may interfere with the evaluation of glaucoma.

Our findings during ketamine anesthesia agree with those of Peuler[8] and of Harris.[10] However, differences in methodology and age distribution do not permit direct quantitative comparisons. Corssen[7] also reported similar IOP values during ketamine anesthesia, but the results of that study represent a small (2 torr), but statistically significant, increase in IOP. The greatest increase in IOP was found by Purschke and Hassouna,[5] who reported an increase of 34 torr 15 minutes after ketamine administration.

The inconsistency of previous studies evaluating ketamine action may be related, in part, to differences in premedication and the methods of tonometry. The MacKay-Marg applanation tonometer is generally considered more accurate than the indentation tonometers used in many of the previous studies.

We conclude that in the absence of endotracheal intubation, ketamine does not raise IOP in the healthy pediatric patient and, therefore, can be used for ophthalmic procedures requiring sedation or anesthesia.

REFERENCES

1. Ausinsch B, Graves SA, Munson ES, et al: Intraocular pressures in children during isoflurane and halothane anesthesia. Anesthesiology 42:167-172, 1975

2. Dominguez A, Sanchez Banos M, Gimenez Alvarez M, et al: Intraocular pressure measurement in infants under general anesthesia. Am J Ophthalmol 78:110-116, 1974

3. Radtke N, Waldman J: The influence of enflurane anesthesia on intraocular pressure in youths. Anesth Analg 54:212-215, 1975

4. Yoshikawa K, Murai Y: The effect of ketamine on intraocular pressure in children. Anesth Analg 50:199-202, 1971

5. Purschke RI, Hassouna I: Der Einfluss von Ketamin auf den intraokularen Druck. Z Prakt Anaesth 8:227-231, 1973

6. Adams A: Ketamine in paediatric ophthalmic practice. Anaesthesia 28:212-213, 1973

7. Corssen G, Hoy JE: A new parenteral anesthetic—CI-581: its effect on intraocular pressure. J Pediat Ophthalmol 4:20-23, 1967

8. Peuler M, Glass DD, Arens JF: Ketamine and intraocular pressure. Anesthesiology 43:575-578, 1975

9. Hilton GF, Shaffer RN: Electronic applanation tonometry. Am J Ophthalmol 62:838-843, 1966

10. Harris JE, Letson RD, Buckley J: The use of CI-581, a new parenteral anesthetic, in ophthalmic practice. Trans Am Ophthalmol Soc 66:206-213, 1968

Anesthesia and the Modification of Response to Infection in Mice

PETER G. DUNCAN, MD*
BRUCE F. CULLEN, MD†
NANCY N. PEARSALL, PhD‡
Seattle, Washington§

Anesthetic-induced immunosuppression, if clinically significant, could modify the natural course of infectious diseases *in vivo*. To test this hypothesis, the localized response to IM *Candida albicans* and the mortality following fecal peritonitis were examined in anesthetized mice. Using these 2 models, halothane anesthesia was found not to modify the natural history of local sepsis but to significantly accentuate the mortality associated with the more severe infection. Possible explanations for these results include significant inhibition of reticuloendothelial function or plasma opsonization with relatively minor derangements of peripheral leukocyte capability.

ANESTHESIA and surgery are associated with suppression of various components of the immune response.[1,2] Anesthesia may reduce bacterial phagocytosis and killing, impair lymphocyte transformation, and alter immunoglobulin production in appropriate *in vitro* assay systems. However, the significance of these observed defects to the *in vivo* resistance to infection remains to be determined. The immune system has many effector mechanisms which tend to overlap in the intact individual, thus compensating for an isolated deficiency in a single component. In addition, immune responses are often far greater than needed to control an invading organism, suggesting that the deficiency must be quantitatively large or the infection unusually great before adverse effects will be noted. The present studies were undertaken to determine what role, if any, anesthesia plays in the host response to infection *in vivo*.

We studied the influence of halothane in the pathogenesis of 2 types of infections in mice: (A) *Candida albicans*, injected into the mouse thigh, and (B) suspended colonic contents, injected intraperitoneally (IP). The former produced an easily measured lesion, self-limited over 4 to 6 weeks, the size of the abscess appearing to be dependent upon host vascular and granulocytic responses with little evidence for the participation of specific cell-mediated immune mechanisms.[3] This model thus afforded an accurate assessment of host resistance to a localized infection *in vivo*. In contrast, fecal peritonitis, as previously reported,[4] was associated with a more generalized infection and a high mortality rate.

*Research Fellow, Department of Anesthesiology.
†Associate Professor, Department of Anesthesiology.
‡Associate Professor, Department of Microbiology and Immunology.
§University of Washington, Seattle, Washington 98195.

This study was supported in part by NIH (NIGMS) Grants #GM-15991 and #DE 02600-08 and the Canadian Medical Research Council.

Dr. Duncan's current address: Department of Anesthesiology, Health Sciences Centre, 700 William Avenue, Winnipeg, Manitoba, Canada.

Paper received: 3/3/76
Accepted for publication: 4/7/76

METHODS AND MATERIALS

A. Candida Albicans Model.—The test organism, *C albicans*, obtained from the Department of Microbiology and Immunology, University of Washington, was passaged regularly on Sabouraud's agar. Organisms to be injected were grown for 24 to 48 hours in Sabouraud's broth at 37° C, centrifuged from the broth, washed 3 times in saline solution, counted, and resuspended in saline at a concentration of 2.5×10^8 viable yeast cells per milliliter.

The left thigh of 78 male outbred Swiss-white mice weighing 25 to 35 gm was injected IM with 25×10^6 organisms/gm body weight, suspended in 0.2 ml of physiologic saline. The right thigh was injected with 0.2 ml saline as a control. Thigh size was measured with sliding calipers daily for the first 10 days as the lesions developed, then at intervals until the lesion had regressed completely. The largest dimension was taken as the thigh size and was recorded as the difference from the control side for each animal.

Test animals were divided into 4 groups:

Group I: Halothane administered for 4 hours immediately before infection (n=14).

Group II: Halothane administered for 4 hours immediately after infection (n=10).

Group III: Halothane administered for 4 hours daily for 4 days before infection (n=9).

Group IV: Halothane administered for 4 hours daily for 4 days after infection (n=20).

One control group, similarly infected and paired for each test group, received 100 percent O_2 according to the same schedule, while a 2nd control group was maintained in air.

Animals were anesthetized in a 30 x 14 x 34-cm plexiglass container. Halothane was administered in 100 percent O_2 at a rate sufficient to maintain ambient halothane concentration at 1.1 ± 0.1 percent. Total gas flow was 3 L/min. Halothane, O_2, and CO_2 concentrations were monitored by a Beckman LB-II infrared gas analyzer, a Beckman DB-2 paramagnetic analyzer, and an Instrumentation Laboratories gas analyzer, respectively. Rectal temperatures were maintained at 37 ± 0.5° C by an overhead heat lamp. A maximum of 20 animals were anesthetized at any one time, and all anesthetics were administered at a similar time of day.

Following anesthesia, the mice were allowed to recover in O_2 until capable of a sustained righting response, after which they were housed in similar cages for the duration of the experiment. Animals were given food and water ad lib; daily weighing indicated no gross metabolic alteration secondary to the anesthetic.

To examine the effect of halothane on *C albicans* itself, cultures prepared with 5×10^8 organisms in Sabouraud's broth were incubated for 4 hours daily for 4 days in either 1 percent halothane, 100 percent O_2, or air. The remainder of the time, the cultures were maintained in air at 37° C. At the end of the 4 days, the yeast cells were counted in a hemocytometer.

B. Fecal Peritonitis Model.—Fecal material was obtained from male Swiss-Webster mice by irrigating the colons with 20 ml of Hank's balanced salt solution (HBSS) immediately after death. The fecal material was homogenized with a tissue grinder and the resulting suspension filtered through surgical gauze. Mice of the same strain were injected IP with 0.7 ml of the fecal suspension, using a 23-gauge needle. Control (noninfected) animals received a similar volume of HBSS without colonic contents. Forty additional mice were injected with a similar preparation which had been heat-sterilized at 100° C for 60 minutes, leaving endotoxin and particulate matter in the suspension.

Infected animals were paired into 2 groups and subjected to either 0.6 to 0.8 percent halothane in O_2 or to 100 percent O_2 for 4 hours by the anesthetic technic described above, with no more than 20 animals treated in a single experiment, to a total of 6 paired studies. Food and water were withheld for 12 hours from both groups upon recovery from anesthesia, to offset any metabolic advantage to the unanesthetized controls.

These mice were distributed into 5 groups:

Group I: Halothane administered for 4 hours after IP injection of fecal suspension (n=48).

Group II: O_2 administered for 4 hours after IP injection of fecal suspension (n=46).

Group III: Halothane administered for 4 hours after IP injection of HBSS (n=20).

Group IV: Halothane administered for 4 hours after IP injection of heat-sterilized fecal suspension (n=20).

Group V: O_2 administered for 4 hours after IP injection of heat-sterilized fecal suspension (n=20).

Mortality was assessed regularly for the next 2 weeks, after which the survivors were sacrificed and gross examination of the peritoneum was made.

Statistics.—Results of the mouse thigh lesion were examined by Student's *t*-test for unpaired data. Mortality in the fecal peritonitis model was evaluated by chi-square with continuity correction.

RESULTS

A. Mouse Thigh Lesion.—The administration of halothane was not associated with any significant alteration in the magnitude of the IM lesion produced by *C albicans*. Similarly, there was no significant alteration in the time course of development or regression of the abscess. Data for group IV (figure) are representative of all other groups. Similar results were obtained with other dosage schedules, none of which demonstrated any significant difference in size of the control thighs with time or within groups; hence, the diameter of the infected side is recorded in absolute figures.

The administration of halothane, even on consecutive days, did not affect the weight of the animals despite apparent lethargy for several hours after anesthesia. Halothane did not affect the growth of *C albicans in vitro*, for cell counts were similar after exposure to the anesthetic gas, O_2, or air.

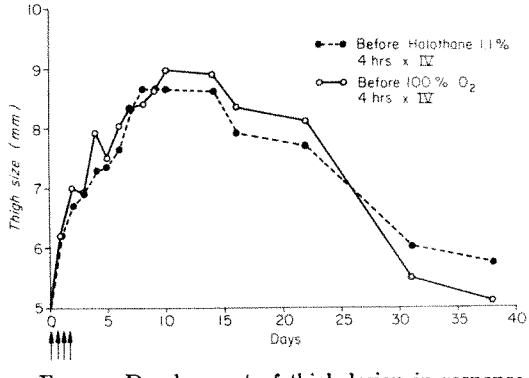


FIGURE. Development of thigh lesion in response to IM *C albicans* in mice of group IV. Similar results were obtained for the other groups in thigh tests.

TABLE 1
Anesthetic Mortality Due to Infection

	HBSS, n = 20	Infected, n = 48	*p*
Deaths	0	3	≤0.1
Percent mortality	0	6	

B. Fecal Peritonitis Model.—The administration of halothane to mice infected with colonic contents was associated with increased mortality during the anesthetic period; hence, 0.6 to 0.8 percent halothane was employed rather than the 1.1 percent concentration used in the mouse thigh model. Although the difference was not statistically significant, mortality during a single exposure to halothane was 6 percent for infected animals as compared to none for control animals anesthetized without infection (table 1).

Since the animals that died during anesthesia appeared to develop copious airway secretions and respiratory obstruction as a terminal event, they were excluded from subsequent calculations, as they did not represent morality directly attributable to the infection. The following data therefore represent only those animals that recovered from anesthesia and survived the acute cardiopulmonary consequences of halothane imposed on septicemia.

Following halothane-O_2 anesthesia, mice with peritonitis exhibited a significantly increased mortality as compared with O_2-treated mice. This was apparent from 24 hours after anesthesia to the end of the study at 14 days (table 2). Mean mortality from 6 paired experiments was 44 percent in O_2 as compared to 81 percent in halothane. Heat sterilization of the colonic contents prevented mortality in O_2-treated mice and greatly reduced mortality in halothane-treated animals (table 3). Thus the effect of halothane was significant only when mice were infected with viable organisms. In both halothane and O_2, the use of viable organisms significantly increased mortality over that observed with endotoxin-containing killed suspensions alone.

The bacterial species isolated from the fecal suspension were predominately *Escherichia coli* and enterococci, as determined by standard isolation technics. Cultures for

TABLE 2
Mortality From Fecal Peritonitis
(Excluding Anesthetic Mortality)

Time after anesthesia	Oxygen (n = 46)		Halothane (n = 45)		p
	Deaths*	% Mortality†	Deaths*	% Mortality†	
3 hr	0	0	0	0	—
16 hr	19	38 ± 18	23	47 ± 15	NS
24 hr	19	38 ± 18	28	59 ± 11	0.05
36 hr	20	40 ± 18	34	77 ± 6	0.005
48 hr	21	44 ± 16	35	79 ± 6	0.005
72 hr	21	44 ± 16	36	81 ± 7	0.005
14 days	21	44 ± 16	36	81 ± 7	0.005

*Deaths expressed as total for all experiments.
†Percent mortality expressed as mean (± SE) for 6 experiments.
NS = not significant.

TABLE 3
Mortality From Intraperitoneal Endotoxin
(Excluding Anesthetic Mortality)

Time after anesthesia	Oxygen (n = 20)		Halothane (n = 17)		p
	Deaths	% Mortality	Deaths	% Mortality	
3 hr	0	0	1	6	NS
16 hr	0	0	1	6	NS
24 hr	0	0	1	6	NS
36 hr	0	0	2	12	NS
48 hr	0	0	2	12	NS
72 hr	0	0	2	12	NS
14 days	0	0	2	12	NS

strict anaerobes were not performed. Both experimental and control animals received equal aliquots of the fecal suspension. Thus, although the quantity of bacteria per injection was not determined, it was identical for paired anesthetized and control animals.

DISCUSSION

While anesthetic-induced immunosuppression has been demonstrated by *in vitro* technics, the impact of these findings on the prognosis of patients bearing infections has not been well documented. In particular, it is not known whether similar derangements occur *in vivo*. Animal models have been used previously to study infection during anesthesia, but results have been inconclusive.

Bruce[5] demonstrated an accelerated mortality in mice subjected to halothane anesthesia after IP injection of *Salmonella typhimurium*, although the ultimate mortality of his anesthetized animals was similar to control. Goldstein's group,[6] using radiolabeled *Staphylococcus aureus*, found impaired murine pulmonary bactericidal activity following cyclopropane and methoxyflurane administration but not after halothane or pentobarbital. However, their mice were sacrificed immediately after anesthesia, leaving open to question the significance of observed results in the development of pneumonia. Viral pneumonia is more easily produced in mice under ether anesthesia,[7] although this has been attributed to altered host respiratory mechanics rather than to immunosuppression by the anesthetic. Hence, it remains to be demonstrated experimentally that anesthetic agents alone are capable of significantly modifying the morbidity or mortality associated with microbial invasion.

Our studies suggest that halothane anesthesia in the presence of severe infection (peritonitis) is associated with increased mortality, although the precise mechanism remains to be elucidated. On the other hand, localized infection with organisms of low virulence (*C albicans*) does not appear to be significantly modified by halothane anesthesia.

The mouse immune system is very similar to that of man; hence, it affords a reasonable experimental model for the study of infectious diseases. The mouse thigh lesion appears to be a valid *in-vivo* technic for assessment of immune responses to *C albicans*, with the development of the lesion principally a function of the neutrophil response. The modification of the normal response in the thigh lesion by antibiotics and

steroids[8] parallels the clinical picture of candidiasis in animals and man.

Peripheral leukocytes have the primary responsibility in control of local sepsis.[9] Failure of halothane to affect the size of the lesion produced in response to candida suggests that this anesthetic has little effect on the mobilization and deposition of inflammatory cells at an infected site, at least with *C albicans* as the inciting organism. Whether similar responsiveness persists in intact animals subjected to other organisms remains to be determined. Bruce,[5] in contrast, demonstrated reduced mobilization of neutrophils into the peritoneal cavity of mice in response to salmonella infection during halothane anesthesia. His results, however, may be attributed to altered splanchnic blood flow caused by this anesthetic and not necessarily to reduced leukocyte capability.

In contrast to its failure to affect the development of a localized abscess, halothane significantly increased the lethality of fecal peritonitis in the model we employed. Failure of heat-sterilized fecal material to have a similar effect suggests that death was the result of active infection rather than an indirect effect of endotoxin. Since mortality was increased well after anesthesia was discontinued, and since deaths occurring during anesthesia were excluded, it is doubtful that any acute cardiovascular or respiratory effects of the anesthetic can be incriminated.

Before attributing these results to altered host defense mechanisms, it is necessary to rule out effects of the anesthetic on the microorganism's growth characteristics. We were unable to demonstrate any inhibition or stimulation of fungal growth by halothane *in vitro*. Previous authors[10] have documented growth inhibition of bacteria by halothane for species such as *E coli*, but at concentrations achievable only in anesthetic apparatus.[11] In addition, the effects appear to be less significant on moist, protein-rich agar than on dry cellulose-acetate media, suggesting that *in vivo* effects should be minimal at the scene of an inflammatory exudate.[12] The increased O_2 administered with halothane may inhibit anaerobic growth, but this we controlled by using O_2-treated controls. Hence, we conclude that direct antimicrobial effects of halothane should be minimal in our experimental situation.

In response to generalized bacterial infection and septicemia, the phagocytic cells of the reticuloendothelial system (both fixed and circulating) and polymorphonuclear leukocytes control the infectious process.[9] Their activities are promoted by opsonins, circulating proteins which react with bacteria to cause their easier phagocytosis and destruction. Opsonins in serum include natural antibodies, immune antibodies, components of the complement system, and yet-unidentified thermolabile proteins. Certain organisms, such as *E coli*,[13] are relatively resistant to phagocytosis unless they are suitably opsonized.

It is postulated, though by no means proved, that the increased mortality following anesthesia was in part the result of depressed reticuloendothelial phagocytic function, whereas normal host defense mechanisms remained intact in control animals. Surgery in animals is associated with a reduced reticuloendothelial capability,[14] probably due to reduced plasma opsonization.[15] While peripheral leukocytes do not appear to be affected by halothane,[16,17] the phagocytic ability of the reticuloendothelial system is impaired in humans undergoing minor surgery with a variety of anesthetics, including halothane.[18] It may be that the organisms of our model were potentiated by halothane-induced suppression of reticuloendothelial phagocytosis or by modification of normal serum opsonization. Such mechanisms are only speculative at present, to be explored by further studies.

Anesthesia is all too often accompanied by side effects, such as hypoxia, acidosis, and hypothermia, all of which have been shown to diminish bactericidal ability in experimental animals.[6,19] Although our animals were anesthetized in 100 percent O_2 and kept normothermic, some degree of acidosis probably occurs in all anesthetized small animals that must breathe spontaneously.[20] In addition, there is some evidence that infected animals may be abnormally susceptible to the cardiovascular and respiratory-depressant effects of anesthesia.[21] This latter point may explain the increased incidence of respiratory complications in the infected mice and consequent elevated intra-anesthetic mortality.

It is a time-honored impression that patients with infections fare poorly after anesthesia, although firm evidence supporting this contention is lacking. Anesthesia is associated with increased morbidity and mortality in patients bearing the infectious hepatitis virus,[22] an observation paralleled by the increased ease of induction of viral

hepatitis in mice subjected to halothane.[23] Respiratory infections are frequent after both general[24] and topical[25] anesthesia, usually attributed to altered respiratory mechanics and impaired mucociliary clearance. Whether other pathogens can similarly be potentiated by anesthesia remains to be demonstrated.

CONCLUSIONS

We have demonstrated an increased mortality (to 81%) in mice subjected to anesthesia after IP injection of fecal material sufficient to kill 44 percent of control animals. Anesthetic complications were also increased in infected animals. While the localized inflammatory response to *C albicans* IM is not affected by halothane, effects of the anesthetic or complications thereof on other aspects of host defenses, particularly on reticuloendothelial function, remain to be excluded.

ACKNOWLEDGMENT

We thank Marlene Risen for excellent technical assistance during the studies of *Candida albicans*.

The halothane used was generously provided by Ayerst Laboratories.

REFERENCES

1. Bruce DL, Wingard DW: Anesthesia and the immune response. Anesthesiology 34:271-282, 1971

2. Moudgil GC, Wade AG: Anaesthesia and immunocompetence. Br J Anaesth 48:31-39, 1976

3. Pearsall NN, Lagunoff D: Immunological responses to Candida albicans. I. Mouse thigh lesion as a model for experimental candidiasis. Infect Immun 9:999-1002, 1974

4. Weinstein WM, Onderdonk A, Bartlett J, et al: Experimental intra-abdominal abscesses in rats: development of an experimental model. Infect Immun 10:1250-1255, 1974

5. Bruce DL: Effect of halothane anesthesia on experimental salmonella peritonitis in mice. J Surg Res 7:180-185, 1967

6. Goldstein E, Munson E, Eagle C, et al: The effects of anesthetic agents on murine pulmonary bactericidal activity. Anesthesiology 34:344-352, 1971

7. Dubin IN: The role of ether anesthesia in the production of influenza virus pneumonia in mice. J Immunol 51:355-357, 1945

8. Thompson REM: Effects of antibiotics and steroids on the growth of Candida in vitro and in vivo. Symposium on Candida Infections. Edited by WI Winner, R Hurley. Edinburgh, E & S Livingstone, 1966, pp 65-71

9. Alexander JW: Host defense mechanisms against infection. Surg Clin North Am 52:1367-1378, 1972

10. Barry PP, Paiement B, Dubeau M: Recherche sur l'activité antibacterienne de certains agents anesthésiques. Can Anaesth Soc J 11:640-644, 1964

11. Wardley-Smith B, Nunn JF: The effect of halothane on bacterial growth rate. Br J Anaesth 43:919-924, 1971

12. Mehta S, Beher G, Kenyon D: The effect of volatile anaesthetics on bacterial growth. Can Anaesth Soc J 20:230-240, 1973

13. Stossel TP: Phagocytosis. N Engl J Med 290:717-723, 1974

14. Scovill W, Saba TM: Hepatic reticuloendothelial host defense failure following surgical trauma. Arch Surg 110:954-959, 1975

15. Saba TM: Mechanism mediating reticuloendothelial system depression after surgery. Proc Soc Exp Biol Med 133:1132-1136, 1970

16. Cullen BF: The effect of halothane and nitrous oxide on phagocytosis and human leukocyte metabolism. Anesth Analg 53:531-536, 1974

17. Cullen BF, Hume RB, Chretien PB: Phagocytosis during general anesthesia in man. Anesth Analg 54:501-504, 1975

18. Löfström B, Schildt B: Reticuloendothelial function under general anaesthesia. Acta Anaesthesiol Scand 18:34-40, 1974

19. Eisele J, Goldstein E, Martucci R, et al: The influence of acute respiratory acidosis on the pulmonary defense mechanisms in rats. Am Rev Respir Dis 108:218-224, 1973

20. White PF, Johnston RR, Eger EI II: Determination of anesthetic requirements in rats. Anesthesiology 40:52-57, 1974

21. Milas L: Anaerobic corynebacteria and anesthetics. Lancet 1:695-696, 1975

22. Harville D, Summerskill W: Surgery in acute hepatitis. JAMA 184:257-261, 1963

23. Moudgil GC: Influence of halothane on mortality from murine hepatitis virus. Br J Anaesth 45:1236, 1973

24. Webster AC, Taylor F, Lucas B: Isotope mucociliary clearance: an investigation of the effects of anesthetic agents on mucociliary flow. Abstracts of Scientific Meeting. Washington, DC, American Society of Anesthesiologists Annual Meeting, 1974, pp 185-186

25. Corssen G: Toxic effect of local anaesthetics on human respiratory epithelium. Can Anaesth Soc J 20:17-20, 1973

The Effects of Stellate Ganglion Block on the Idiopathic Prolongation of the Q-T Interval with Cardiac Arrhythmia (The Romano-Ward Syndrome)

HISASHI YANAGIDA, MD*
CHIYUKI KEMI, MD†
KUNIO SUWA, MD‡

The association of a prolonged Q-T interval, congenital deafness, and syncopal attacks due to ventricular fibrillation following emotional or physical stress is known as the Jervell-Lange-Nielsen syndrome. Absence of the congenital deafness characterizes the otherwise identical Romano-Ward syndrome. Both conditions have a high mortality rate and are recognized as contributing to sudden death in children. Although the pathogenetic factors are not yet completely elucidated, the condition is well enough understood to permit effective treatment. The authors performed a left stellate ganglion block in a 12-year-old girl with a mild form of the Romano-Ward syndrome, shortening the Q-T interval and eliminating the ventricular tachyarrhythmia. The left stellate ganglion block should be considered by anesthesiologists as an emergency measure, effective in interrupting the attack.

THE association of a prolonged Q-T interval, congenital deafness, and syncopal attacks due to ventricular fibrillation following emotional or physical stress is a clinical entity known as the Jervell-Lange-Nielsen syndrome.[1] Absence of the congenital deafness characterizes the otherwise identical "Romano-Ward" syndrome.[2,3] Both conditions (long Q-T syndrome) have a high mortality rate and are recognized as contributing to sudden death in children.[4]

The pathogenesis of long Q-T syndrome is dependent on an imbalance between various components of the cardiac sympathetic innervation. A congenital decreased activity through the right cardiac sympathetic nerves seems the most likely pathogenetic mechanism in the majority of cases.[5-8] Other forms of sympathetic imbalance, including left or even right hyperactivity, are, however, possible in isolated cases.[9]

Beta-blockers, at full blocking dose, represent the therapy of choice and are greatly effective in reducing mortality.[9] If medical therapy is not effective, ablation of the left stellate ganglion along with the first thoracic ganglia is the most rational and specific therapy.[5,6,9,10]

CASE REPORT

We performed a left stellate ganglion block in a 12-year-old girl, diagnosed as having a mild form of Romano-Ward syndrome. She was admitted to the hospital because of attacks of dizziness and cardiac arrhythmia, the latter having been noted since birth. At age 11, she experienced a feeling of sudden fullness in the chest, dizziness, and acute abdominal discomfort for about 2 minutes. Seven months later, she cried out and fell unconscious, although neither cyanosis nor convulsions occurred. Subsequently, she had similar attacks with increasing frequency, often, though not constantly, related to emotional or physical stress. Recovery, after about 2 minutes, was associated with headache and nausea. She felt otherwise well and

*Chief Anesthesiologist, Department of Anesthesiology and Electroencephalography, Yokohama Teishin Hospital, Yokohama, Japan.

†Associate, Department of Anesthesiology, Tokyo University Hospital, Tokyo, Japan.

‡Associate Professor, Department of Anesthesiology, Tokyo University Hospital, Tokyo, Japan.

Paper received: 11/17/75
Accepted for publication: 3/1/76

her vital signs remained normal. She had not taken any drugs.

Physical examination showed essentially normal findings. The heart was normal on palpation. The heart sounds were normal but the rhythm was irregular. No third or fourth heart sounds or murmur were present. The heart rate was 70 bpm, blood pressure 115/80 torr supine, and 110/85 torr standing. Arterial and venous pulses were normal but irregular. Chest radiography was normal.

Hemodynamic Studies.—Left ventricular systolic time constants were studied with the aid of simultaneous electrocardiogram, phonogram, carotid pulse tracing, and apex cardiogram. The pre-ejection period was 101 msec, the left ventricular ejection time 313 msec, and the isovolumetric relaxation period 106 msec, the heart rate being 54 cycles/min. All these values are within the range considered normal in this laboratory. After these studies, the heart was catheterized, to exclude the remote possibility of silent idiopathic cardiomyopathy. The left ventricular end-diastolic pressure (LVEDP) was 9 torr. No gradient was present in the left ventricular outflow tract or at the aortic valve. The aortic pressure pulse wave was normal. The left ventricular cineangiogram revealed a ventricular cavity of normal size, a ventricular myocardium of normal size and thickness, and a normal synergic pattern of contraction, with normal cardiac and stroke indices.

Other laboratory investigation, which included urinalysis, serum glucose tolerance test, intravenous ethylene-ediaminetetraacid test to exclude hypoparathyroidism, catecholamine, metanephrine, and adrenaline excretion during bed rest and while ambulatory, electroencephalogram, and audiogram revealed no abnormalities.

Family Studies.—Examination of parents and brothers revealed no abnormalities. Cardiac disease had caused the death of the patient's paternal grandmother and one of 6 paternal grand-uncles, but no syncopal attacks were reported. Four of 6 paternal cousins had clinically observable cardiac arrhythmias but showed no Q-T prolongation on the ECG.

Electrocardiographic Studies.—The ECG recorded in the supine position at rest showed normal P waves, P-Q interval, QRS complexes, and a consistently prolonged Q-T (or Q-U) interval, which varied between +38 to +29 percent of the predicted normal value at each heart rate encountered. In the tracing recorded in the supine position, it was not possible to differentiate between the T and U waves, which together produced a common complex (fig 1).

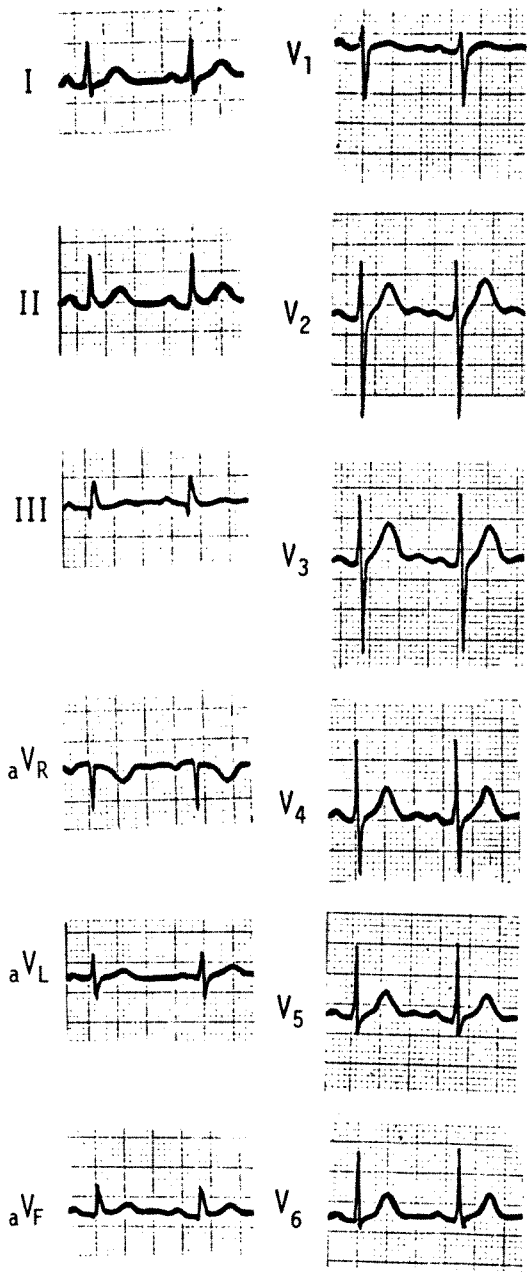


FIG 1. Supine decubitus ECG, heart rate 85 (extremity), 88 (precordial), showing normal P waves, P-Q interval, QRS complex, and S-T segments, and prolonged Q-T interval (0.4 sec versus normal of 0.31 and 0.29 sec).

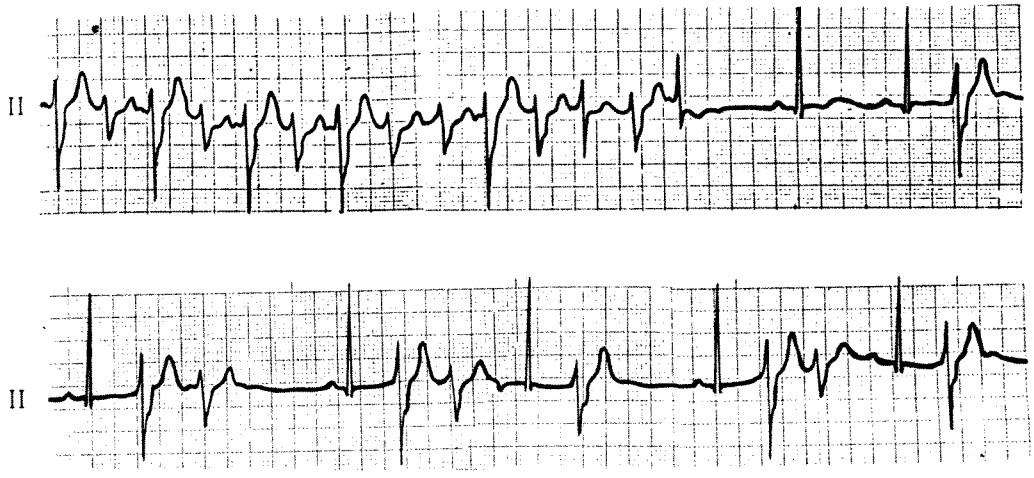


FIG 2. Upper tracing: During attack, supine decubitus ECG, showing paroxysmal ventricular arrhythmias. At that time, patient complained of fullness in the chest. The Q-T interval is prolonged (0.66 sec, upper limit of normal 0.45 sec at heart rate of 61 to 65 bpm). Lower tracing: An exercise ECG showing paroxysmal ventricular arrhythmias.

According to a 12-hour continuous ECG decubitus recording, the sinus rhythm (fig 1) never continued for over 1 minute but showed paroxysmal ventricular arrhythmias (fig 2, upper tracing). The abnormally long Q-T interval persisted (about +47 percent of the predicted normal). At that time she complained of a sense of fullness in the chest. A Master's two-step ECG produced paroxysmal ventricular arrhythmias (fig 2, lower tracing) after 10 seconds. These ventricular arrhythmias with prolongation of Q-T interval did not respond to medical therapy by digitalis, propranolol, atropine, diphenylhydantoin, or phenobarbital.

Left Stellate Ganglion Block. — In the ECG (fig 3A) taken immediately before the left stellate ganglion block, the abnormal Q-T interval can be plainly seen. Block with 5 ml of 1 percent lidocaine shortened the Q-T interval for about 10 minutes and eliminated the ventricular arrhythmia for 35 minutes (fig 3B). By 5 minutes after block, the Q-T interval became minimum. At that time, Horner's syndrome appeared maximum, as did the amplitude of plethysmogram recorded from the left thumb. Table shows the time courses of the changes in Q-T interval after left stellate ganglion block. These effects were reproducible.

DISCUSSION

The association of a prolonged Q-T interval and syncopal attacks following emotional or physical stress represents a dramatic and unmistakable clinical picture. If congenital deafness and/or episodes of alternation of the T wave occur, the diagnosis is even easier. The seriousness of long Q-T syndrome, however, is not the same in all patients: While some patients may have many syncopal attacks per month, others have a few per year, and still others have only one or two episodes in their entire lives.[9]

Moreover, syncope is not always associated with the Romano-Ward syndrome, a mild form of which includes transient palpitations, a feeling of fullness in the chest, apprehension, sweating, guarding of the abdomen, moaning, and crying.[10] Our present case is probably of a mild form in the Romano-Ward syndrome. The possible mode of inheritance has been largely discussed in several papers.[12,13] However, all recognize the finding of patients whose immediate relatives have no deafness or other familial pattern of signs or symptoms.

The long Q-T syndrome is provoked by abrupt increase in the sympathetic activity, which is likely to be nonuniform and mostly mediated through the left sympathetic upper thoracic ganglia.[9] It follows, as already suggested,[9] a double therapeutic line: one less specific consisting of the treatment with beta-blockers, and one more specific consisting of the ablation of left stellate ganglion along with the first thoracic ganglia.

In our present case, propranolol had no effect on the ventricular arrhythmia and Q-T interval, leading to the belief that surgical treatment is the most rational choice. As our patient refused surgical removal of

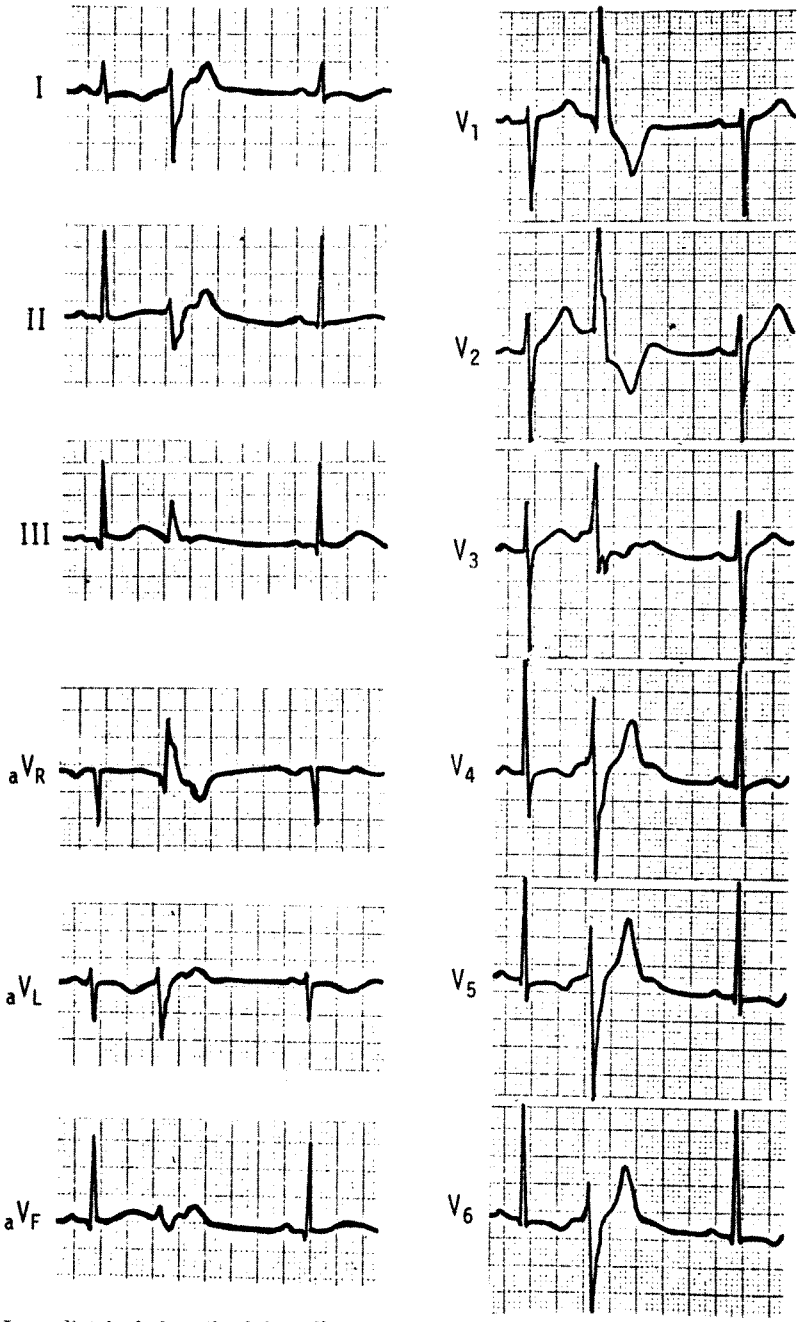


FIG 3. A. Immediately before the left stellate ganglion block, ECG recorded in decubitus supine patient.

the left stellate ganglion, left stellate ganglion block, in place of surgical removal, resulted in a definite shortening of the Q-T interval for about 10 minutes and in the disappearance of ventricular arrhythmia for 35 minutes.

Moss and MacDonald[5] obtained a Q-T prolongation with right stellate ganglion block and a shortening with left stellate ganglion block. Dear* observed no change in the Q-T interval after either left stellate ganglion or right stellate ganglion block. Furthermore, several authors found a prolongation of the Q-T interval both left and right stellate ganglion block.†[13] It was also reported that left stellate ganglion block in the cat was shown to produce significant

*Dear W: Personal communication, 1974.

†James TN: Personal communication, 1974.

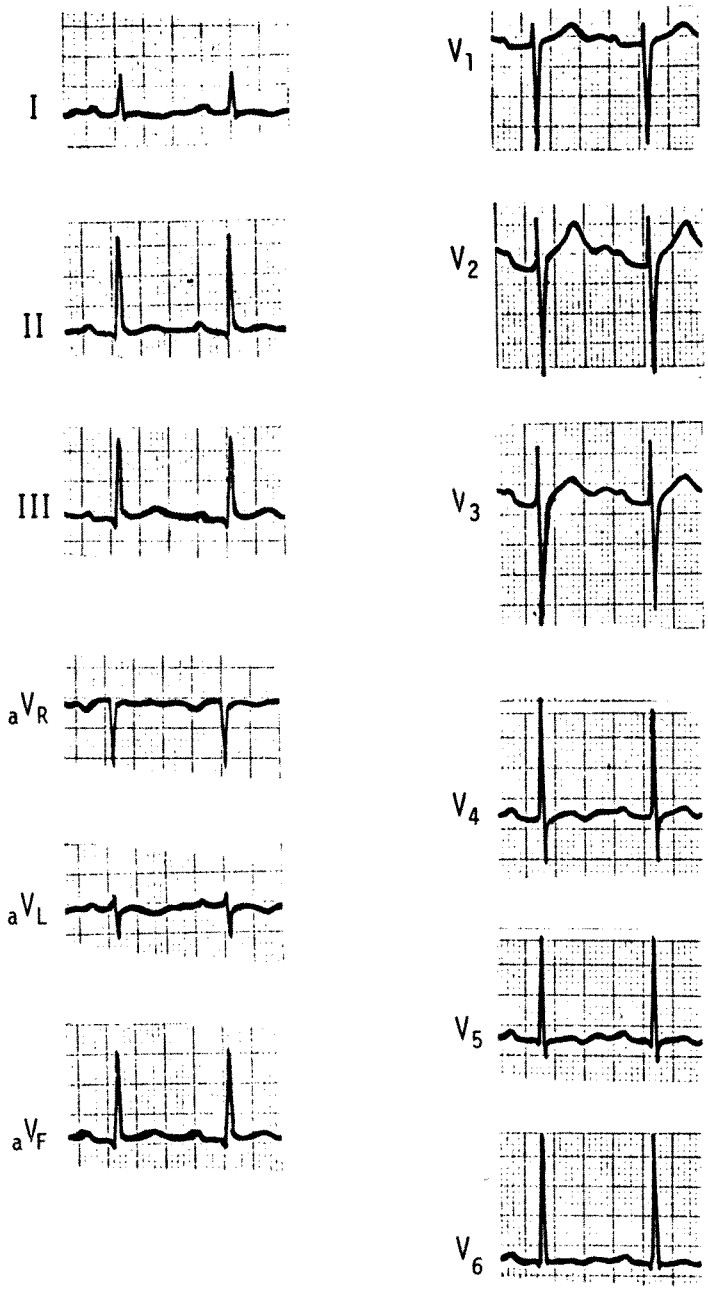


FIG 3. B. Ten minutes after left stellate ganglion block. ECG recorded in decubitus supine patient. The Q-T interval is apparently shortened (0.36 sec, upper limit of normal 0.39 sec at heart rate of 81 bpm).

prolongation of the functional refractory period exclusively in the lateral and posterior left ventricle.[14] Randall and Rohse[15] showed that the left stellate ganglion mediates mainly inotropic effects while the right stellate ganglion mediates mainly chronotropic effects.

Stellate ganglion block is not a simple maneuver. Usually performed through a blind procedure, there can be no certainty about the exact spread of the anesthetic. Moreover, performance of this procedure under local anesthesia is likely to frighten the patient, resulting in increased sympathetic activity. An attempted left stellate ganglion block can even lead to a prolongation of the Q-T interval as a result of increased discharge through the ganglion, or from mechanical stimulation by the needle.

TABLE

Q-T Intervals Calculated by Bazett's Formula $QT/\sqrt{R\text{-}R}=0.368$ Upper Limit of Normal 0.45 sec at Heart Rate of 60 Beats per Minute.

	Q-T interval (sec.)
Before	0.64
1 min.	0.48
2	0.45
5	0.41
10	0.42
15	0.53
25	0.51
30	0.53

The appearance of Horner's syndrome is sometimes believed to be the mark of an effective stellate ganglion block and, therefore, of a block of cardiac nerves: On the contrary, it only indicates blockade of the fibers which traverse the upper part of the stellate ganglion, and may or may not be accompanied by effective blockade of fibers innervating the heart. In our present case, the effects of a left stellate ganglion block were reproducible but it was a short effect (about 10 minutes), with incomplete blockade of cardiac fibers.

Despite such difficulties, knowledge of the effectiveness of stellate ganglion block as an emergency measure in interrupting the threat of a long Q-T syndrome may prove life-saving in patients with Romano-Ward symptoms.

REFERENCES

1. Jervell A, Lange-Nielsen F: Congenital deaf mutism, functional heart disease with prolongation of the Q-T interval and sudden death. Am Heart J 54:59-68, 1957

2. Romano C, Genrme G, Pongiglion R: Aritmie cardiache rare dellétà pediatrica (Presentazione del primo case della lattertura pediatrica italiana). Clin Paediatr 45:656, 1963

3. Ward OC: New familial cardiac syndrome in children. J Ir Med Assoc 54:103, 1964

4. Fraser GR, Froggatt P: Unexpected cot deaths. Lancet 2:56-57, 1966

5. Moss AJ, MacDonald J: Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long Q-T interval syndrome. N Engl J Med 285:903-904, 1971

6. Schwartz PJ, Malliani A: Electrical alternation of the T-wave: clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long Q-T syndrome. Am Heart J 89:45-50, 1975

7. Olley PM, Fowler RS: The surdo-cardiac syndrome and therapeutic observations. Br Heart J 32:467-471, 1970

8. James T: Congenital deafness and cardiac arrhythmias. Am J Cardiol 19:627-643, 1967

9. Schwartz PJ, Periti M, Malliani A: The long Q-T syndrome. Am Heart J 89:378-390, 1975

10. Fraser GR, Froggatt P, James TN: The congenital deafness associated with electrocardiographic abnormalities, fainting attacks, and sudden death. Q J Med 33:361-385, 1964

11. Fraser GR, Froggatt P, Murphy T: Genetical aspects of the cardio-auditory syndrome of Jervell and Lange-Nielsen (congenital deafness and electrocardiographic abnormalities). Ann Hum Genet 28:133-157, 1964

12. Mathews EC Jr, Blount AW Jr, Townsend JI: Q-T prolongation and ventricular arrhythmias. with and without deafness, in the same family. Am J Cardiol 29:702-711, 1972

13. Vincent GM, Abildskov JA, Burgess MJ: Q-T interval syndromes. Prog Cardiovasc Dis 16: 523-530, 1974

14. Rogers MC, Abildskov JA, Preston JB: Cardiac effects of stimulation and block of the stellate ganglion. Anesthesiology 39:525-533, 1973

15. Randall WC, Rohse WG: The augmentor action of the sympathetic cardiac nerves. Circ Res 4:470-475, 1956

The Development of an Acute Tolerance to Ketamine

JAMES F. CUMMING, MD, PhD*

A rapidly developing tolerance to the hypnotic effect of ketamine in rats and mice has been investigated. On the basis of plasma and brain concentrations of ketamine at the time the animals wakened, it seemed likely that a central nervous system tolerance to the drug explained the shortened sleeping times noted.

THE rapid development of tolerance to central nervous system (CNS) depression by a number of drugs has been reported. Drugs with which this effect has been associated include, among others, ethyl alcohol,[1] pentobarbital,[2] thiopental,[3,4] glutethimide,[5] and diazepam.[6] Two of the effects noted were a shortened sleeping time following repetition of the same dose of the drug, and an increase in the blood level required to produce an observed effect. Mirsky's group,[1] in 1941, described this latter type of acute tolerance to ethanol in the rabbit and in man, and Brodie and colleagues,[3] a decade later, showed that in the human, thiopental plasma levels on waking were higher after a large dose of the drug than after a smaller one. An acutely developing tolerance to the effect of thiopental on the rate of cerebral O_2 consumption has been described.[7]

For the past several years, a new short-acting IV anesthetic agent, ketamine, has been in clinical use. Animal experiments showed that, in monkeys, repeated injections to a total of 6 did not result in a change in sleeping time.[8] Extensive clinical experience seemed to indicate that repeated injections of the drug required little change in dosage and were not followed by any change in observed anesthetic time.

While we were investigating this drug for possible enzyme inductive effects, a sharp decrease in the sleeping time of rats consequent to the 2nd injection of the drug was observed. The abrupt onset suggested a rapidly developed tolerance. We have investigated this possibility.

MATERIALS AND METHODS

Animal Experiments.—Male rats weighing between 190 and 250 gm, obtained from a local supplier,† were housed in air-conditioned quarters and fed *ad libitum* on standard laboratory feed. Groups of rats were given IP injections of ketamine (90 mg/kg), and their sleeping times measured from loss to regaining of the righting reflex. One group received only the initial injection, and from these brain and plasma samples were obtained at the time of recovery of the righting reflex. The samples were analyzed for ketamine concentration. Other groups were allowed to recover and then further injections of ketamine (90 mg/kg IP) were given at 5, 6, 24, 48, and 72 hours following the 1st injection. Brain and plasma samples were obtained at the time of recovery of the righting reflex at each time interval. All the animals used in a sequence of experiments came from the same shipment lot.

Another set of experiments on male rats used a dose of 80 mg/kg IP of ketamine. These animals were tested only for sleeping time at 24-hour intervals to a total of 5 exposures.

Other sleeping time studies used male mice of 20 to 30 gm weight given ketamine (100 mg/kg IP). Sleeping time was recorded after the 1st, 2nd, 3rd, and 4th injections, administered at 24-hour intervals.

Chemical Analyses.—Ketamine concentrations in plasma were estimated as previously described.[9] Brain samples were assayed by making a 25 percent homogenate

†Simonson, St. Paul, Minnesota.

*Assistant Professor of Anesthesiology and Pharmacology, Department of Anesthesiology, University of Minnesota Health Sciences Center, Minneapolis, Minnesota 55455.

Paper received: 12/19/75
Accepted for publication: 2/6/76

TABLE

Sleeping Time, Brain and Plasma Levels of Ketamine and Brain to Plasma Concentration Ratio of Ketamine at Recovery of Righting Reflex in Male Rats Given Ketamine (90 mg/kg IP) at the Indicated Times

Injection number	Time of injection, hours	n	Sleeping time ± SEM, min	n	Brain concentrations of ketamine on recovery of righting reflex ± SEM, μg/g	n	Plasma concentrations of ketamine on recovery of righting reflex ± SEM, μg/ml	Brain/plasma ratio of ketamine
1	0	47	23.7 ± 1	18	12.04 ± 0.79	17	2.84 ± 0.25	4.25
2	24	39	17.4 ± 1*	24	13.73 ± 0.78†	24	3.68 ± 0.27*	3.74
3	48	18	14.1 ± 1*	12	14.15 ± 1.3†	13	4.3 ± 0.63*	3.3
4	72	5	16.2 ± 2.9*	5	15.34 ± 3.36†	5	3.59 ± 0.35*	4.27

*Differs from 1st injection $p<0.05$.

†Differs from 1st injection $p<0.1$.

(w/v) of brain in KCl 1.15 percent. To 6 ml of the homogenate was added 3 ml of 20 percent metaphosphoric acid. This was shaken on a vortex mixer, then centrifuged. Supernatant (5 ml) was placed in a reaction vessel containing 15 ml of chloroform and 20 μg of pheniramine maleate as an internal standard. NaOH (10 N) 0.5 ml was added to make the mixture strongly alkaline. From this point, treatment was as described earlier[9] for the assay of ketamine in plasma. Standard curves were constructed for each day's determinations from the results of known concentrations of ketamine in brain homogenate subjected to the same procedure. The peak height ratio of ketamine to internal standard related linearly to ketamine concentrations.

RESULTS

The results of repeated injections of ketamine into rats at 24-hour intervals for 4 successive doses are summarized in the table. Sleeping time decreased abruptly (26%) between the 1st and 2nd doses. A further but lesser decrease occurred between the 2nd and 3rd exposures. The decrease in sleeping time was accompanied by an increase in the brain and plasma ketamine levels at the time of wakening. Differences between initial values of each parameter and subsequent values at each exposure were significant, as indicated in the table. The brain/plasma ratio at wakening showed an initial decrease, but returned to its original value on the 4th exposure.

Figures 1 and 2 illustrate the changes in sleeping time and brain and plasma ketamine levels on waking between the 1st exposure and a repeated injection at 5 and at 6 hours. When a 2nd injection of ketamine was given 5 hours after the 1st, the animals slept a significantly longer time following

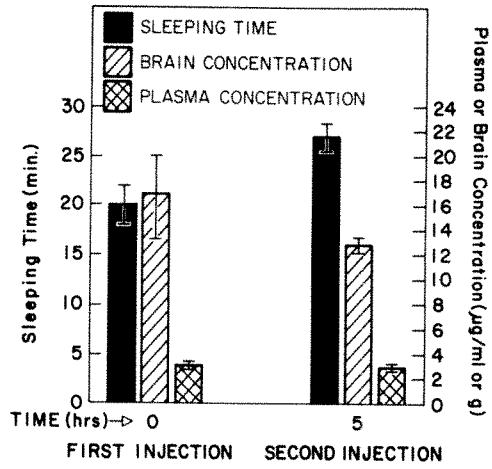


FIG 1. Sleeping time, waking brain and plasma concentration of ketamine in rats following the 1st and 2nd injections of ketamine (90 mg/kg IP) 5 hours apart.

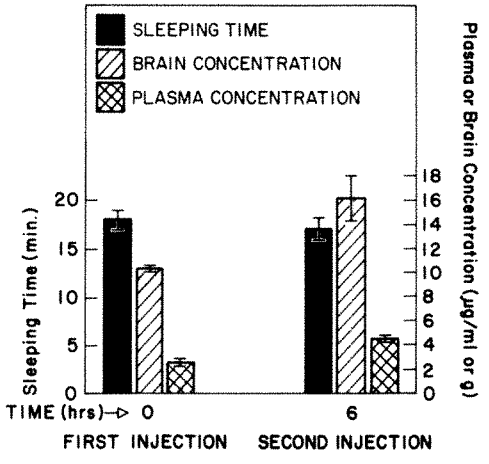


FIG 2. Sleeping time, waking brain and plasma concentration of ketamine in rats following the 1st and 2nd injections of ketamine (90 mg/kg IP) 6 hours apart.

the 2nd injection ($p<0.025$). The waking brain and plasma levels after the 2nd exposure were not different than after the 1st ($p<0.2$, $p<0.3$). When the 2nd injection was given 6 hours after the 1st, sleeping time was now decreased slightly. The difference between overall means was not significant, but between values where a paired *t*-test was possible, the difference was highly significant ($p<0.025$). Waking brain and plasma levels were significantly higher than after the 1st injection ($p<0.01$).

Figure 3 illustrates the effect of consecutive injections of ketamine, 80 mg/kg IP, on the sleeping time of rats. The decline in sleeping time noted, particularly between the 1st and 2nd injections, is similar to that noted when a dose of 90 mg/kg IP was given.

Mice respond to repeated injections of ketamine in a manner paralleling the response of rats (fig 4). Sleeping time decreases sharply between the 1st and 2nd doses and also between the 2nd and 3rd doses. The sleeping time after the 4th dose, however, is not significantly different than that after the 2nd dose.

DISCUSSION

The development of an acute tolerance to ketamine, evident in the present work, and to other CNS depressants reported elsewhere by others,[1-7] could be explained in various ways: by an increase in ability to biotransform the agent; by an alteration in the blood-brain barrier to the drug; or by an increase in resistance of CNS cells to the effect of the drug. An alteration in ability to biotransform the drug seems unlikely, since the onset of induction of drug-metabolizing enzymes is a relatively slow process compared with the rapid onset of the acute tolerance witnessed here. Early work done at the Parke-Davis Company* also showed that repeated parenteral doses of ketamine HCl administered to rats did not increase the *N*-demethylating capacity of the hepatic microsomal enzymes. Further, if a more rapid metabolism were the cause, there is little reason to expect a change in waking plasma and brain concentrations of the drug. A change in the blood-brain barrier is possible, but does not seem likely in view of the very rapid onset of anesthesia in all species given the drug IV.

The table does show some variation in the brain/plasma ratio between control and previously exposed animals. The deviations do not explain the higher waking brain concentrations of ketamine in the latter animals, and the ratio returns to that of the control animals at a time when the animals are still sleeping a shorter time and waking with higher brain concentrations. A change in blood-brain barrier would not be expected to alter the waking brain concentrations of the drug. By contrast, if the neurons of the CNS became rapidly resistant to the effect of the drug, a higher plasma and brain level on waking would be expected. This explanation would seem to fit best the data presented here.

Rapidly developing accommodation to the CNS effects of many sedatives and hypnotics has been reported. In Mirsky's investigation of the effect of ethanol in the rabbit and in man,[1] the effect of the drug in both

*Unpublished data.

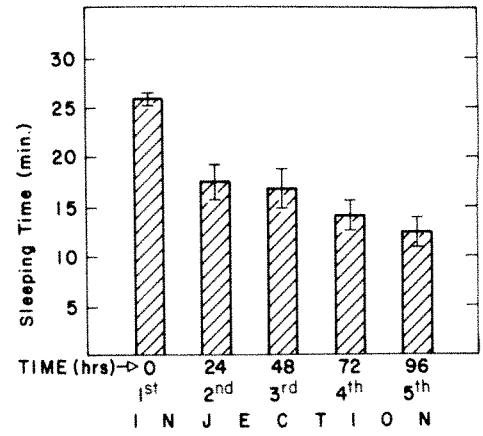


FIG 3. Sleeping time of rats following 5 successive doses of ketamine (80 mg/kg IP) at 24-hour intervals.

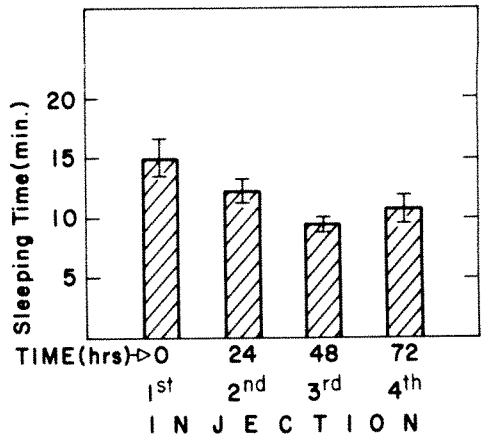


FIG 4. Sleeping time of mice following 4 successive doses of ketamine (100 mg/kg IP) at 24-hour intervals.

species (coma in the rabbit, drunkenness in man) disappeared while blood levels of ethanol were considerably above those noted at the onset of the effect. In both species, repeated administration of the drug showed that higher levels were required to produce the same effect at each subsequent exposure. In the rabbit, the repetition could be carried to several exposures, each resulting in a further rise of blood ethanol at which symptoms disappeared.

The work presented in this paper demonstrates a similar response. As shown in the table and in figures 3 and 4, subsequent exposures to ketamine in both rats and mice resulted in progressively shorter sleeping times to at least 3 administrations. A similar response to repeated injections of thiopental was noted in the male rat by Singh.[10] These observations all indicate that the limit of tolerance is not reached after 1 or even 2 moderate doses of the drugs used. Larger doses appear to elicit a greater response. This conclusion was also indicated in earlier work by Brodie[3] and by Dundee's group.[4]

Barnett and Fiore[6] showed the development of a tolerance to diazepam in cats by testing the linguomandibular reflex. Their experiments indicated the tolerance was due to a metabolite of diazepam, which presumably had a good affinity for the same CNS receptors as diazepam, but had a much weaker agonist effect and therefore acted as a partial antagonist to diazepam.

In the experiments here, a similar explanation might pertain. The biotransformation products of ketamine are presumed to be pharmacologically inactive, and they are also excreted in both urine and feces. The original investigative work by the Parke-Davis Company* showed that about 74 percent of an IP dose in the rat appeared in the urine and feces by 24 hours (as measured by radioactivity). It therefore seems unlikely that competition for receptor sites by an inactive metabolite would explain the shortened sleeping time observed in this work, following subsequent doses of ketamine at 24-hour intervals. Such an explanation might be postulated for the tolerance which developed by 6 hours.

The time required to demonstrate a tolerance in this work was 6 hours. Animals reinjected at 5 hours slept longer than after their 1st exposure (fig 2). It is possible that there was a residual effect from the 1st dose still present by 5 hours which could account for the increased sleeping time. The data presented here do not suggest any definite mechanism. At 6 hours after an initial dose, a 2nd dose of ketamine resulted in a shortened sleeping time, apparently by a mechanism of CNS tolerance to the drug, since the animals were waking with higher brain and plasma levels of ketamine (fig 3). Singh[10] reported that a minimum of 4 hours was required for female rats to develop tolerance to thiopental, a time quite similar to that observed here.

This work demonstrates a rapidly developing tolerance to the CNS-depressant effect of ketamine. The degree of the tolerance is of modest dimension, but was demonstrated in rats at 2 different dosage levels and in a different species (mice). The tolerance to ketamine resembles the tolerance to a number of other CNS depressants and seems to represent an unidentified adaptation of CNS neurons which permits them to accommodate to the presence of a depressant drug.

*Unpublished data.

REFERENCES

1. Mirsky JA, Piker P, Rosenbaum M, et al: Adaptation of the central nervous system to varying concentrations of alcohol in the blood. Q J Stud Alcohol 2:35-45, 1941

2. Aston R: Acute tolerance indices for pentobarbital in male and female rats. J Pharmacol Exp Ther 152:350-353, 1966

3. Brodie BB, Mark LC, Lief PA, et al: Acute tolerance to thiopental. J Pharmacol Exp Ther 102:215-218, 1951

4. Dundee JW, Price HL, Dripps RD: Acute tolerance to thiopentone in man. Br J Anaesth 28: 344-352, 1956

5. Curry SH, Norris H: Acute tolerance to a sedative in man. Br J Pharmacol 38:450P-451P, 1970

6. Barnett A, Fiore JW: Acute tolerance to diazepam in cats and its possible relationship to diazepam metabolism. Eur J Pharmacol 13:239-243, 1971

7. Altenburg BM, Michenfelder JD, Theye RA: Acute tolerance to thiopental in canine cerebral oxygen consumption studies. Anesthesiology 31: 443-448, 1969

8. McCarthy DA, Chen G, Kaump DH, et al: General anesthetic and other pharmacological properties of 2-(o-chlorophenyl)-2-methylamino cyclohexanone HCl (CI 581). J New Drugs 5:21-33, 1965

9. Lo JN, Cumming JF: Interaction between sedative premedicants and ketamine in man and in isolated, perfused rat livers. Anesthesiology 43: 307-312, 1975

10. Singh JM: Clinical signs and development of tolerance to thiopental. Arch Int Pharmacodyn 187:199-208, 1970

Lorazepam Premedication: Lack of Recall and Relief of Anxiety

ROBERT J. FRAGEN, MD*
NANCY CALDWELL, CRNA†
Chicago, Illinois‡

Premedication with lorazepam (4 mg), diazepam (10 mg), and a placebo was compared in a randomized, double-blind study of 95 adult surgical patients. Comparisons were made of recall of a memory card and events of the operative day, relief of anxiety, degree of somnolence, effects on blood pressure and heart rate, and incidence of side effects. Lorazepam produced a significant lack of recall (antegrade amnesia) compared to the other agents. Lorazepam produced a greater antianxiety effect than placebo and a greater degree of somnolence than diazepam or placebo. Since no adverse effects on blood pressure or heart rate occurred, lorazepam appears to show promise as a premedicant.

UPON arrival in the operating room, the patient should be calm and sedated, yet alert enough to be cooperative. Amnesia for the events of the operative day is also desirable. Premedicant drugs are commonly used to achieve these goals. They may in turn produce cardiorespiratory depression. With these points in mind, we compared lorazepam, a newer benzodiazepine, with diazepam and a placebo for preanesthetic medication. Premedication is usually given intramuscularly by a nurse on the hospital ward. Therefore, this route was chosen, although previous studies of oral[1] and IV[2] lorazepam premedication have been reported.

The widely used 1,4 benzodiazepines, chlordiazpoxide and diazepam, have the desirable premedicant properties of hypnosis, sedation, anxiolysis, antegrade amnesia, and a wide margin of safety.[3,4] Lorazepam, a newer member of this group of drugs, has the above properties but supposedly differs from diazepam in its longer duration of action and greater production of antegrade amnesia.[1] Diazepam (10 mg) IM has been shown to produce antegrade amnesia in 3 percent of patients.[4] Diazepam (0.24 mg/kg) IV was shown to produce a short period, 10 to 20 minutes, of lack of recall on all patients tested.[5] Lorazepam given IV for premedication produced a significant lack of recall at 3 mg, but 5 mg was associated with a high incidence of side effects.[2]

Evaluation of the efficacy of premedication is both subjective and objective. The patients' anxiety, apprehension, and state of consciousness and cooperation can be rated by both observer and patient. An important subjective measure is the patient's degree of recall of the event and his overall impression of the experience.[6] This concept was used in our study.

METHODS

After obtaining informed consent,§ 95 adult surgical patients, who verbalized anxiety about their forthcoming surgical experience, were admitted to the study. Medication was administered IM in a randomized

§These studies were reviewed and approved by the Northwestern University-Northwestern Memorial Hospital Institutional Review Board.

*Associate Professor.

†Research Assistant.

‡Department of Anesthesia, Northwestern University Medical School, and Northwestern Memorial Hospital, Chicago, Illinois 60611.

Paper received: 2/16/76
Accepted for publication: 3/1/76

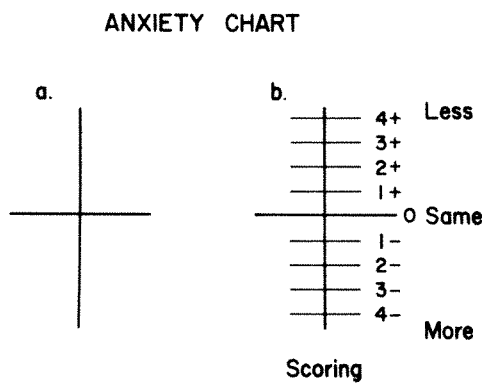


FIG 1. *a*. Chart containing no numbers, shown to patients to measure a change in degree of anxiety. *b*. Chart used to score change in anxiety level, based on point indicated by the patient in *a*. The baseline represents the same level of anxiety; above the baseline, less; below the baseline, more anxiety.

and controlled double-blind experimental design.

Patients were divided into 3 groups: group I received lorazepam (4 mg); group II received diazepam (10 mg); group III received a placebo consisting of benzyl alcohol, polyethylene glycol, and propylene glycol, the vehicle for lorazepam. The only other premedicant used was atropine sulfate (0.4 mg to 0.6 mg), as needed.

Recall was measured by a memory card, a large picture of a dollar bill, shown to the patient 120 minutes after injection. The day following the operation, patients were asked if they could recall this card. If they could not, they were shown a composite picture containing the dollar bill and seven other pictures. They were then asked if they had seen any of these pictures the previous day and whether they could remember certain events of the operative day. These events did not occur at the same interval after injection in all patients.

Relief of anxiety, using the chart shown at *a*, figure 1, was evaluated in the patient's room 60 minutes after injection. The midpoint of the vertical line represented the anxiety level prior to premedication. The patient was then asked to evaluate changes in anxiety by indicating a point on the vertical line. We recorded this point on a similar chart which contained cross-lines (*b*, fig 1) showing percentages of improvement or worsening. These values were then scored respectively as 1+, 2+, 3+, and 4+ or 1–, 2–, 3– and 4–.

The degree of somnolence was rated by one of the investigators (NC) as none, somnolent (drowsy but awake), and markedly somnolent (asleep but arousable). This was evaluated at 60 and 120 minutes postinjection.

A visit was made 24 hours postoperatively at which time patients were asked to evaluate the premedication as excellent, good, fair, or not acceptable; asked if the premedication made them sleepy or drowsy; examined for abnormalities at the injection site; and observed for any other adverse effect. Our impression of the premedication was then rated as satisfactory or unsatisfactory.

Blood pressure was measured by the Riva-Rocci method and heart rate was determined by counting the radial or temporal pulse. These were measured and recorded prior to injection, at 60 and 120 minutes postinjection, prior to induction of anesthesia, during anesthesia, in the recovery room, and at the time of the postoperative visit. Data were compared by chi-square analysis. Lorazepam patients were compared with patients in each of the other groups when analyzing recall data.

RESULTS

The groups were homogeneous for age, weight, height, and sex (table 1) and were

TABLE 1
Demography

	Group I	Group II	Group III
Total number of patients (sex)	32 (12M, 20F)	32 (11M, 21F)	31 (8M, 23F)
Mean age, yr (range)	40.6 (20-64)	41.1 (22-65)	46.8 (23-63)
Mean weight, kg (range)	67 (40-91)	64 (45-91)	66 (42-91)
Mean height, cm (range)	170 (150-188)	165 (152-188)	165 (152-185)

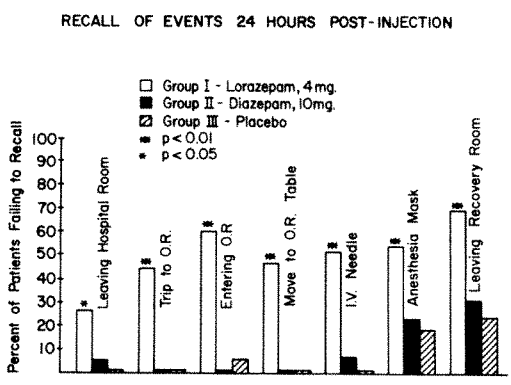


FIG 2. Percent of patients in each group failing to recall specific events of operative day.

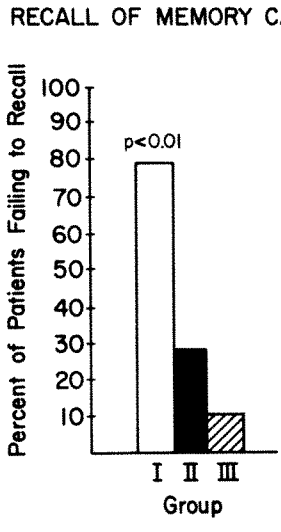


FIG 3. Percent of patients in each group who failed to recall the memory card.

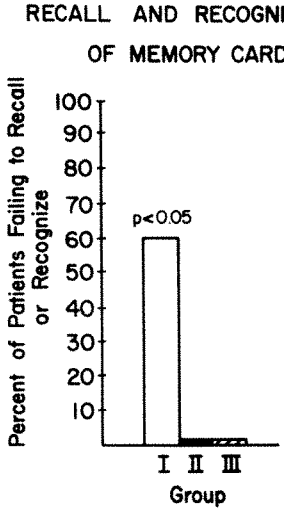


FIG 4. Percent of patients, from figure 3, who did not recall memory card and subsequently did not recognize it in a composite picture.

also homogeneous for race, ASA physical status, anesthetic medications, muscle relaxants, other intraoperative medications received, medications given in the recovery room, and types of surgical procedures.

Some patients who inadvertently received additional benzodiazepine in the operating room were dropped from the study except for the preoperative antianxiety evaluation. Two were dropped from the antianxiety study because they were brought to the operating room before 60 minutes had elapsed.

Approximately half the patients receiving lorazepam failed to recall most of the events of the day of operation (fig 2), while recall in groups II and III was extremely high.

Presentation of the memory card was the only event which occurred at the same interval after injection in all groups. Failing to recall the memory card (fig 3) were 22/29 in group I, 8/29 in group II, and 2/25 in group III. All patients in groups II and III who claimed not to recall the memory card did recognize it in the composite (fig 4). Of group I patients, 13/29, or 45 percent, failed both to recall the memory card and to recognize it in the composite.

Anxiety scores and the cumulative percent of patients at each score or higher were compared by patients and groups (table 2). A statistically significant difference was seen when lorazepam was compared with placebo ($\chi^2 = 5.003$, $p<0.05$). No difference

TABLE 2
Anxiety Scores
(60 minutes postinjection)

Anxiety scores	Group I Lorazepam, 4 mg IM	Group II Diazepam, 10 mg IM	Group III Placebo IM
+4	2 (7)	1 (3)	1 (3)
+3	4 (20)	3 (12)	1 (6)
+2	11 (55)	11 (46)	6 (26)
+1	7 (78)	5 (62)	6 (46)
0	6 (97)	11 (96)	15 (96)
1−	1 (100)	1 (100)	0 (96)
2−	0	0	1 (100)
Median score	+2	+1	0
Total number of patients	31	32	30

( ) Cumulative percent of total.

TABLE 3
Physician's Evaluation of Somnolence

Time of evaluation	Degree of somnolence	Group I Lorazepam, 4 mg IM	Group II Diazepam, 10 mg IM	Group III Placebo IM	χ^2	p value
60 minutes during anxiety testing	No somnolence	16 (55.2)	24 (82.8)	20 (95.2)		
	Somnolent	5 (17.2)	5 (17.2)	1 (4.8)	18.37	0.001
	Marked somnolence	8 (27.6)	0	0		
120 minutes at time memory card was shown	No somnolence	17 (58.6)	27 (93.1)	21 (100)		
	Somnolent	9 (31.0)	2 (6.9)	0	8.41	0.001
	Marked somnolence	3 (10.4)	0	0		

( ) Percent of total in group.

TABLE 4
Patient Acceptance of Premedication

	Group I Lorazepam	Group II Diazepam	Group III Placebo
Excellent	15/29	8/29	5/25
Good	11/29	15/29	10/25
Satisfactory	2/29	2/29	1/25
Unsatisfactory	1/29*	4/29†	9/25†

*Considered unsatisfactory because injection was painful.

†Considered unsatisfactory because not calm when brought to OR.

was seen in comparing diazepam with either lorazepam or placebo.

No marked somnolence was seen in groups II and III at 60 and 120 minutes (table 3). Group I patients were sleepier than those in either of the other groups but were able to cooperate on command. When patients were asked the next day if the premedication made them sleepy or drowsy, 17/29 in group I said "yes," while this was true of only 7/29 patients in group II and 6/25 patients in group III.

Patient acceptance of lorazepam premedication was high, 26/29 rating it as excellent (15) or good (11) (table 4). We judged 27/29 patients in group I, 25/29 in group II, and 14/25 in group III to have satisfactory premedication. Patients were judged to have unsatisfactory premedication if they appeared nervous when entering the operating room. Thus, lorazepam and diazepam both produced objectively satisfactory sedation in a significantly higher ($p<0.01$) percentage of patients than did placebo, but did not differ between themselves.

Similar blood pressure and heart rate changes occurred in each group of patients and no change was great enough to require treatment. No adverse effects attributable to premedication were seen in any patient in the preoperative period or during the postoperative period the day of operation.

DISCUSSION

The most striking feature of lorazepam is lack of recall of events occurring between 1½ and 6 hours after injection. About 50 percent of the patients receiving lorazepam had amnesia for most events. The event having less recall than other concurrent events, for groups II and III, was showing the anesthesia mask. Leaving the recovery room was also poorly remembered, probably due to the combination of premedication, anesthetic agent residual, and postoperative medication effects. Recall was greatest when a long time elapsed between lorazepam injection and entrance to the operating room.

The dollar-bill picture has been shown to be a strong stimulus to memory,[2] yet 45 percent of the lorazepam patients had total amnesia for this memory card, as demonstrated by lack of recall and lack of recognition from the composite picture. This was not so for any patients in the other groups. Diazepam did not demonstrate any more amnesic effect than placebo. Inability to recall events of the operative day was a desirable property and none of the patients felt unfavorably about this when seen 24 hours later. Patient acceptance was greater for lorazepam.

Is lack of recall a desirable property of a drug? Not all patients may want amnesia, if they know they can undergo an operation without pain. Further, it may be considered disadvantageous to have retrograde or prolonged amnesia. This and previous

studies[1,6] have shown that lorazepam produced only antegrade and not prolonged amnesia.

While objective measurements are too involved to be used in this type of study, lorazepam (4 mg) was shown to be anxiolytic at least to the same degree as diazepam (10 mg) and superior to placebo. The number of patients claiming some relief of anxiety correlates well with the number rating the medication excellent or good in each group.

Since more patients claimed relief of anxiety than were somnolent at 60 minutes postinjection, relief of anxiety appears to be a different effect from somnolence in some patients. The greatest degree of somnolence was seen 60 minutes postinjection, in older patients and in those of small stature. Although somnolence was greater with lorazepam, more patients in each group thought they were somnolent than were observed to be.

Despite lorazepam's long duration of action, no patient had adverse circulatory or respiratory effects in the recovery room or during the first postoperative day. When premedication is ordered "on call," the patient may be brought to the operating room before the medication has time to act. Its effects may either complicate, or be masked by, anesthesia. Premedication with lorazepam well in advance of induction would obviate this problem and is feasible, due to its long duration of action.

REFERENCES

1. Wilson J, Ellis FR: Oral premedication with lorazepam (Ativan): a comparison with heptabarbitone (Medomin) and diazepam (Valium). Br J Anaesth 45:738-744, 1973

2. Heisterkamp DV, Cohen PJ: The effect of IV premedication with lorazepam (Ativan), pentobarbitone or diazepam on recall. Br J Anaesth 47:79-81, 1975

3. Dundee JW, Haslett WHK: The benzodiazepines: a review of their action and uses relative to anaesthetic practice. Br J Anaesth 42:217-234, 1970

4. Dundee JW, Haslett WHK, Keilty SR, et al: Studies of drugs given before anaesthesia. XX: diazepam-containing mixtures. Br J Anaesth 42: 143-150, 1970

5. Clarke PRF, Eccersley PS, Frisby JP, et al: The amnesic effect of diazepam (Valium). Br J Anaesth 42:690-697, 1970

6. Greenblatt DJ, Shader RI: Benzodiazepines in Clinical Practice. New York, Raven Press, 1974, p 198

ESOPHAGEAL OBTURATOR. The esophageal obturator airway (EOA) may offer a useful approach to ventilation management during cardiopulmonary resuscitation. To quantitate its usefulness arterial blood gases were measured in 18 apneic patients ventilated with an EOA in place. PaO_2 greater than 64 torr (F_IO_2 0.4-1.0) was achieved in 11 of 12 patients with supraventricular cardiac rhythms and greater than 77 torr in 3 of 6 patients still requiring external cardiac massage at the time of measurement. Arterial oxygenation did not improve significantly following tracheal intubation but there was a trend for $PaCO_2$ to decrease as compared with ventilation via the EOA. The adequate oxygenation achieved in most patients suggests that the EOA is a useful adjunct to cardiopulmonary resuscitation when tracheal intubation is not feasible. *(Schofferman J, Oill P, Lewis AJ: The esophageal obturator airway. Chest 69:67-71, 1976)*

Isoenzymes of Creatine Phosphokinase in Serum of Families with Malignant Hyperpyrexia

HERBERT Y. MELTZER, MD*
SHAKEELA Z. HASSAN, MD†
PAUL RUSSO‡
HYONG WON CHO, PhD§
Chicago, Illinois‖

The activity and isoenzymes of creatine phosphokinase (CPK) in the serum of 2 women vulnerable to malignant hyperpyrexia were studied. Serum CPK activity was markedly elevated but, in contrast to a previous report, only skeletal-muscle type CPK activity was present.

VULNERABILITY to malignant hyperpyrexia (MH) can be determined by estimation of serum creatine phosphokinase (CPK) activity.[1,2] However, because of the many possible causes of elevated serum CPK, including intramuscular injections, physical activity, trauma, and alcoholism, it is hazardous to rely too heavily on determinations of serum CPK activity in assessing vulnerability to MH. Examination of pathologic changes in skeletal-muscle fiber and of subterminal motor nerves may be of value, but such changes are nonspecific[4-7] and examination of subterminal motor nerves is not routinely feasible.

There are 3 major isoenzyme types of CPK: skeletal-muscle, cardiac-muscle, and brain type, each so named because of the organs in which they are most abundant.[8] The report of Zsigmond's group[9] of excessive levels of brain-type CPK in the serum of 21/23 individuals possibly vulnerable to MH and in skeletal muscle of 8/9 such individuals is therefore of considerable importance. In no other disease has brain-type CPK been reported to be so persistently present in serum.

Anido and associates[10] found large amounts of brain-type CPK in the serum of 3 patients during episodes of MH, when serum CPK activity was greatly increased. This is to be expected because of the massive brain and muscle damage. However, they did not study serum CPK isoenzymes in people vulnerable to MH. Small amounts may be transiently present after severe brain trauma.[11] Indeed, it has recently been reported,[12] and we have confirmed,[13] that brain-type CPK is unstable in serum both *in vitro* and *in vivo*, being rapidly converted

*Professor of Psychiatry.

†Associate Professor of Anesthesiology.

‡Research Assistant.

§Research Associate.

‖Departments of Psychiatry and Anesthesiology, University of Chicago Pritzker School of Medicine, Chicago, Illinois 60637.

This study was supported in part by USPHS MH 16,127 and MH 25,116. Dr. Meltzer is recipient of the USPHS Career Scientist Award MH 47,808.

Paper received: 9/12/75
Accepted for publication: 3/1/76

to a species which migrates like skeletal-muscle type CPK during electrophoresis. Nealon and Henderson[14] reported that brain-type CPK is unstable at the temperatures used for incubation to detect enzyme activity following electrophoresis. We therefore studied the mechanism by which brain-type CPK was stabilized in serum of MH-vulnerable patients. We have found no published confirmations of Zsigmond's report[9] that brain-type CPK is present in the serum or muscle of such patients.

SUBJECTS AND METHODS

We located only 1 family with documented familial MH, 1 member of which has been previously described.[15] In brief, a male member in 3 generations of this family has expired with muscle rigidity and high fevers during or immediately after operation. *In vitro* study of a skeletal-muscle biopsy specimen from 1 member of the family revealed the development of excessive muscle tension in response to caffeine, with or without halothane, a phenomenon characteristic of MH.[15] We obtained serum samples from that member, age 44, her sister, age 41, her mother, age 69, and her daughter, age 19. The father and brother of these sisters died with MH, as did the son of one of them.

CPK activity was determined by Rosalki's method[16] with reagents from Calbiochem.* The upper limit of normal for white females is 50 mU/ml.[17]

The isoenzymes of serum CPK were studied by 2 methods: (1) Isoenzyme separation was initiated within 1 hour of removing a venous blood sample. The samples were kept at ice-bath temperature prior to use. Three μL of serum were electrophoresed on agarose gels (Pfizer pol-E-film) for 30 minutes and the isoenzymes identified by incubation with Rosalki reagents containing NAD† instead of NADP,‡ and examined for fluorescence.[18] (2) A 1-ml aliquot of serum was used for DEAE-Sephadex-A-50 column chromatographic separation of CPK isoenzymes by the method of Mercer.[19] Rat-brain and skeletal-muscle extracts were studied simultaneously, to assure the reliability of these methods.

RESULTS

Serum CPK activity in the 2 sisters was 351 and 437 mU/ml, respectively. Both levels are sufficiently elevated that concentration of the serum was not considered necessary for separation of the isoenzymes. The serum CPK activity of the daughter and mother was 31 and 29 mU/ml, respectively; they were not further studied.

TABLE

Recovery of Serum CPK Activity in Eluate of DEAE-Sephadex Columns

Sample	CPK activity (mU/ml) Total	Total CPK activity (mU) Fractions 1-2	3-8	9-10
Serum #1	351	306	10	0
Serum #2	437	365	28	0
Brain extract	845	10	50	756
Muscle extract	765	690	0	0

By both electrophoresis and column chromatography, only skeletal-muscle type CPK activity was identified in the serum of both subjects. Not even a faintly fluorescent band was noted in the gels in the region where brain-type CPK fluorescence was present in the brain extracts. Similarly, CPK activity was detectable only in fractions 1 and 2 of the DEAE-Sephadex columns, the region where skeletal-muscle type CPK is expected. Fractions 9 and 10, where brain-type CPK is present, were devoid of activity (table). Brain-type and skeletal-muscle type CPK were readily detected in the brain and muscle extracts.

DISCUSSION

Based on the family history and the study of skeletal muscle response to caffeine in one of these sisters, it seems highly probable that these 2 individuals would be considered typical cases of vulnerability to MH, yet only skeletal-muscle type CPK was present in the serum samples of the 2 sisters. Therefore, the absence of brain-type CPK in their serum cannot be attributed to misdiagnosis, by current criteria. It is conceivable, however, that there is heterogeneity in the group of people vulnerable to MH, such that brain-type CPK is found in the serum of only some people vulnerable to MH.

It is unlikely that a lack of sensitivity in our procedures for identification of brain-type CPK accounted for the difference between our results and those of Zsigmond.[9] We have found* that both the fluorescent

*Calbiochem: CPK Stat-Pack, La Jolla, California 92037.

†Nicotinamide adenine dinucleotide.

‡Nicotinamide adenine dinucleotide phosphate.

*Cho HW: Unpublished results.

method and the DEAE-Sephadex chromatographic method are at least as sensitive for determination of CPK isoenzymes as the tetranitro-blue tetrazolium, phenazine-methosulfate, AMP method employed by Zsigmond. Nonspecific staining can occur with that technic because of the so-called "nothing dehydrogenease reaction,"[18] which can be avoided with the fluorescence method.

It is also unlikely that because of a delay in initiating electrophoresis or column chromatography, the brain-type CPK was transformed into a species resembling skeletal-muscle type CPK described by Frotscher[12] and by Cho.[13] It is not clear from Zsigmond's report whether the serum samples were handled after delay or perhaps frozen prior to use. In either case, brain-type CPK should have been lost rather than gained if transformations took place.

The serum and muscle isoenzymes of CPK of more people vulnerable to MH will have to be studied before the true incidence of brain-type CPK in this disorder is determined; in the meantime, it should not be considered necessary for the diagnosis of MH. Britt* also failed to observe brain-type serum CPK in the serum of an unspecified number of patients with MH. Should brain-type CPK be demonstrable in the serum of MH-vulnerable patients, it would be interesting to investigate the reasons for stability of this ordinarily unstable isoenzyme in their serum.[12,13]

ACKNOWLEDGMENT

The authors wish to thank Dr. Beverly A. Britt for help in locating the patients in this study.

*Britt BA: Personal communication, 8/13/75.

REFERENCES

1. Denborough MA, Hudson MC, Forster JFA, et al: Biochemical changes in malignant hyperpyrexia. Lancet 2:1137-1138, 1970

2. Aldrete JA, Padfield A, Solomon CC, et al: Possible predictive test for malignant hyperpyrexia during anesthesia. JAMA 215:1465-1469, 1971

3. Nevins MA, Saran M, Bright M, et al: Pitfalls in interpreting serum creatine phosphokinase activity. JAMA 224:1382-1387, 1973

4. LaCour D, Juul-Jensen P, Reske-Nielsen E: Malignant hyperthermia during anaesthesia. Acta Anaesthesiol Scand 15:299-317, 1971

5. Schiller HH: Histochemical abnormalities of muscle in malignant hyperpyrexia. Z Neurol 203: 365-369, 1973

6. Harriman DGF, Sumner DW, Ellis FR: Malignant hyperpyrexia myopathy. Q J Med 42: 639-664, 1973

7. Issacs A, Heffron JJA: Morphological and biochemical defects in muscles of human carriers of the malignant hyperthermia syndrome. Br J Anaesth 47:475-481, 1975

8. Burger A, Richterich R, Aebi H: Die Heterogenität der Kreatin-Kinase. Biochem Z 339:305-314, 1964

9. Zsigmond EK, Starkweather WH, Duboff GS, et al: Abnormal creatine-phosphokinase isoenzyme pattern in families with malignant hyperpyrexia. Anesth Analg 51:827-840, 1972

10. Anido V, Conn RB, Mengoli HF, et al: Diagnostic efficacy of myocardial creatine phosphokinase using polyacrylamide disk gel electrophoresis. Am J Clin Pathol 61:599-605, 1974

11. Somer H, Kaste M, Troupp H, et al: Brain creatine kinase in blood after acute brain injury. J Neurol Neurosurg Psychiatry 38:572-576, 1975

12. Frotscher U, Dominik B, Richter R, et al: Die Instabilität der Kreatin-Phosphokinase-Isoenzymes in Serum. Klin Wochenschr 51:801-805, 1973

13. Cho HW, Meltzer HY, Joung JI, et al: Effect of incubation in human plasma on electrophoretic mobility of brain-type creatine phosphokinase. Clin Chim Acta (Submitted for publication)

14. Nealon DA, Henderson AR: Lability of human creatine kinase isoenzymes at 37° C: a complication of electrophoretic separation. J Clin Pathol 28:834-836, 1975

15. Britt BA, Kalow W, Gordon A, et al: Malignant hyperthermia: an investigation of five patients. Can Anaesth Soc J 20:431-467, 1973

16. Rosalki SB: An improved procedure for serum creatine phosphokinase determination. J Lab Clin Med 69:696-705, 1967

17. Meltzer HY, Holy PA: Black-white differences in serum creatine phosphokinase (CPK) activity. Clin Chim Acta 54:215-224, 1974

18. Somer H, Kontinnen A: Demonstration of serum creatine kinase isoenzymes by fluorescent techniques. Clin Chim Acta 40:133-138, 1972

19. Mercer DW: Separation of tissue and serum creatine kinase isoenzymes by ion-exchange column chromatography. Clin Chem 20:36-40, 1974

Naloxone Antagonism After Narcotic-Supplemented Anesthesia

BENJAMIN J. KRIPKE, MD*
ALBERT J. FINCK, MD†
NARENDRA K. SHAH, MD‡
JOHN C. SNOW, MD§
Boston, Massachusetts‖

Narcotic-supplemented balanced anesthesia is increasing in popularity; however, the narcotic must frequently be antagonized postoperatively. Authorities differ in their recommendations as to dose and as to mode and duration of administration of the narcotic antagonist. In the present study of 58 patients undergoing narcotic-supplemented anesthesia, 60 percent of 42 fentanyl patients and 81 percent of 16 morphine patients required postsurgical naloxone for respiratory inadequacy. Naloxone dosage was initially 1.5 μg/kg IV, with repeat IV doses of 1.5 μg/kg, when needed, at 3-minute intervals, until a regular respiratory rate >15 breaths/min was attained. None of the fentanyl patients and only 25 percent (4/16) of the morphine patients required additional naloxone in the recovery room. For the latter, the dose of naloxone previously administered was given IM and proved satisfactory. Additional analgesia was needed by 12 percent (7/58) of the patients during the recovery-room stay. Judicious naloxone titration permitted respiratory adequacy to coexist with analgesia after narcotic-supplemented anesthesia.

THE use of balanced anesthesia, with large doses of opioids to supplement N_2O-O_2, hypnotics, and muscle relaxants, is increasing. Seven factors contribute to the popularity of this procedure: (1) minimal circulatory depression and morbidity with high-risk patients;[1] (2) a nonexplosive anesthetic approach with the expanding intraoperative use of cautery and electronic monitoring; (3) the use of epinephrine for local vasoconstriction; (4) elimination of the risk of renal and hepatic toxicity associated with halogenation and biotransformation of the volatile anesthetics, especially with multiple operations within a short time; (5) facilitation of management of controlled respiration; (6) availability of satisfactory methods for monitoring the degree of patient weakness and assessment of recovery from curare;[2] (7) rapid reversal of narcotic effect with the new antagonist, naloxone.

Various naloxone regimens have been proposed to counter the undesirable respiratory depression associated with large doses of narcotics.[3-5] Our investigation undertook to study the use of naloxone after *moderate* doses of a short-acting narcotic, fentanyl, and a long-acting narcotic, morphine.

MATERIALS AND METHODS

Subjects were 58 adults scheduled for elective nonthoracic surgery and for whom a balanced anesthesia technic was recommended. Informed consent was obtained after consultation.

*Professor and Associate Chairman.
†Associate Professor.
‡Assistant Professor.
§Professor.
‖Department of Anesthesiology, University Hospital, Boston, Massachusetts 02118.

Paper received: 1/6/76
Accepted for publication: 3/10/76

All patients were premedicated with pentobarbital (75 to 100 mg IM) and atropine (0.5 mg IM), 1 to 1½ hours before operation. In addition, they received droperidol to a maximum of 12.5 mg (0.17 mg/kg), thiopental (3 to 4 mg/kg), N_2O-O_2 (3:2), succinylcholine (1 mg/kg) for intubation, and d-tubocurarine (0.3 to 0.5 mg/kg) or pancuronium (0.06 to 0.08 mg/kg) for muscle relaxation. In all patients, the motor response to ulnar-nerve stimulation was evaluated by Block-Aid® monitor. Relaxants were reversed with up to 15 μg/kg of atropine and 35 μg/kg of neostigmine IV, given ± 10 minutes before the end of the surgical procedure.

Forty-two patients received fentanyl (0.35 mg IV) within 20 minutes of induction and 0.05 mg every 20 minutes thereafter or earlier, if clinically warranted, and 16 received morphine (0.5 mg/kg) within 30 minutes of induction. Ventilation was controlled to maintain intraoperative $Paco_2$ between 32 to 36 torr.

At the conclusion of operation, muscle contraction to tetanic stimulation was noted, and N_2O was washed out with 100 percent O_2 for 5 minutes. Subsequently, the patient was tapped on the forehead and called by name. All opened their eyes and breathed on command. If the spontaneous respiratory rate exceeded 15/min, the patient was extubated; otherwise naloxone (1.5 μg/kg) was injected IV every 3 minutes until this rate was achieved.

All patients received humidified O_2 by nasal cannula at 5 to 8 L/min during the recovery-room stay. Pulse rate, indirect blood pressure by cuff, and respirations were recorded every 5 minutes. Nursing routine consisted of dressing observation, positional changes, and patient questioning for pain, every 15 minutes. If pain was present, an analgesic was administered. Hourly, arterial blood was drawn and analyzed for Pao_2, $Paco_2$, pH, and calculated HCO_3.*

All patients were observed for at least 3 hours and received an IM dose of naloxone equal to that which stimulated respiration originally, or 1.5 μg/kg IM if the patient had not received naloxone in the operating room, whenever any of the following conditions existed:

1. Unable to be aroused;
2. Signs of respiratory obstruction;
3. $Paco_2$ >47 torr;
4. Respirations <14/min.

*Model 113, Instrumentation Laboratories, Lexington, Massachusetts.

RESULTS

Patient sex, age, ASA risk, duration of anesthesia, blood loss, and operative site are given in table 1.

The median dose of fentanyl was 0.6 mg (range 0.35 to 1.5), with 0.4 to 1 mg in the 10th to 90th percentile. For morphine, the median dose, range, and 10th to 90th percentile were 36, 15 to 48, and 24 to 45 mg, respectively. These values indicate approximately a 60:1 fentanyl:morphine potency ratio for clinical anesthesia, resembling the 50 to 100-fold potency difference cited elsewhere.[6]

The need to administer naloxone was apparent with either agent (table 2). When fentanyl was used, the need to antagonize was ostensibly related to the time interval between the last dose and termination of

TABLE 1
Characteristics of Patients Given Balanced Anesthesia Supplemented by Either Fentanyl or Morphine

	Fentanyl	Morphine
Sex		
Male	12	7
Female	30	9
Age, years		
13-29	12	1
30-49	20	7
50 and over	10	8
ASA risk		
I	36	6
II	4	8
III	2	2
Duration of anesthesia, hours		
<1½	6	5
1½-3	25	7
>3	11	4
Blood loss, ml		
<100	2	10
100-500	35	4
>500	5	2
Operative site		
Upper abdominal	12	1
Lower abdominal	9	5
Soft tissue	13	5
Bone	8	5

TABLE 2

Percentage of Patients Requiring Naloxone Antagonism After Fentanyl- or Morphine-Supplemented Anesthesia Compared with Interval in Minutes from Last Administration of Narcotic to Completion of Operation

	Fentanyl			Morphine		
		Naloxone required			Naloxone required	
Time, minutes	Total number of patients	Number of patients	Percentage of total	Total number of patients	Number of patients	Percentage of total
<30	11	10	94	3	2	66
30-45	13	10	77	2	2	100
45-60	14	5	35	2	2	100
>60	4	0	0	6	5	83
>120				2	2	100
>180				1	0	

operation. Forty-five minutes after the last dose of fentanyl only 35 percent of patients required naloxone, but after 60 minutes after the last dose of fentanyl, none did. In contrast, the longer duration of action of morphine was evident, as 83 percent of patients required antagonism after more than 1 hour from the last dose.

To achieve the clinical goal of sustained respirations greater than 15/min (table 3), additional increments of 1.5 μg/kg were needed more frequently after morphine (11/13 patients) than after fentanyl (11/25 patients). Circulation was stable throughout the procedures and varied less than 10 percent in both groups.

Patients in both groups were oriented, comfortable, and responsive to command on entrance to the recovery room, and, when not stimulated, all appeared to be asleep but were easily aroused. Much of this effect was attributable to the use of droperidol.

TABLE 3

Total Dose of Naloxone Given Patients Requiring Antagonism After Fentanyl- or Morphine-Supplemented Balanced Anesthesia

	μg/kg naloxone IV			
	1.5	3.0	4.5	6.0
Fentanyl n = 25*	14	9	2	0
Morphine n = 13*	2	8	2	1

*n = number of patients in each group given naloxone. Naloxone was titrated in 1.5 μg/kg increments IV at 3-minute intervals until spontaneous respiratory rate was 15 or more.

Analysis of arterial blood revealed normal values for Pao_2, pH, and calculated HCO_3 during the 3-hour postoperative period of observation. Median $Paco_2$ values for all groups were within normal limits for the 3-hour postoperative period (table 4).

TABLE 4

Hourly Postoperative $Paco_2$ Level Recorded from Narcotic-Supplemented Balanced Anesthesia Patients, Some Given Naloxone Antagonism

		Fentanyl				Morphine			
		Naloxone		No naloxone		Naloxone		No naloxone	
Hours post-operatively	Values	$Paco_2$	Number of patients	$Paco_2$	Number of patients	$Paco_2$	Number of patients	$Paco_2$	Number of patients
1	Median	37	25	34	17	37	13	38	3
	Range	30-43		27-40		30-44		37-47	
2	Median	38	23*	35	15	37	12*	38	3
	Range	30-41		29-41		33-50		35-38	
3	Median	36	22*	35	15	38	11*	38	3
	Range	29-40		28-42		35-47		38-40	

*Patients required narcotic for analgesia.

In the recovery room, 4/16 morphine patients required additional antagonist but none of the 42 fentanyl patients did. The dose required to reverse recurrent narcotization was 1.5 μg/kg IM in 2 cases, and 3 μg/kg IM in the remaining 2.

It is noteworthy that the 2 morphine patients who were successfully treated with the lowest dose of naloxone in the operating room required additional antagonist during the 2nd postoperative hour. Their respirations dropped from 16 to 10 and 9/min, respectively, along with a rise in $Paco_2$ from 42 and 41 torr to 50 and 52 torr, respectively. The remaining 2 who required additional antagonist had similar respiratory changes, their respirations dropping from 16 to 12 and 10/min, respectively, along with a rise in $Paco_2$ from 40 and 43 torr to 47 and 50 torr, respectively. Either marked obtundation or signs of upper respiratory obstruction were associated with the respiratory change. Naloxone IM successfully reversed these signs without further recurrence.

Analgesia persisted well into the recovery period after narcotic-supplemented anesthesia (table 5). Only 5/42 fentanyl and 2/16 morphine patients complained of pain and required additional analgesia. Antagonism with naloxone by titration did not enhance the need for further analgesia.

Postoperative vomiting occurred in only 3/58 patients, 2/42 patients after fentanyl and 1/16 after morphine. Naloxone did not appear to be a causative factor in this regard, since of the 3 who vomited, 2 had received naloxone and 1 had not.

TABLE 5
Number of Patients in Pain Given Additional Narcotic Within the 3-hour Recovery Room Period

	Postoperative hours		
	1	2	3
Fentanyl			
No naloxone (n = 17)	0	2	0
Naloxone (n = 25)	0	2	1
Morphine			
No naloxone (n = 3)	0	0	0
Naloxone (n = 13)	0	1	1

DISCUSSION

Naloxone is the most effective narcotic antagonist currently available. It can completely counteract not only massive narcotic overdose[7] but, in contrast to other antagonists, even therapeutic doses.[8] Further, it can counter overdose by pentazocine,[9] propoxyphene,[10] and the agonistic actions of other narcotic antagonists.[11]

The availability of naloxone has broadened the indications for narcotic-supplemented balanced anesthesia. The major concern with this approach was the prolonged or recurrent respiratory depression arising from either the muscle relaxant or narcotic. The widespead use of the Block-Aid monitor has markedly reduced the difficulties associated with muscle relaxants.[2] Thus, the management of the narcotic must be understood if problems are to be avoided.

Initially, a distinction must be made between a desired state, in which the pharmacologic properties of analgesia, sedation, euphoria, and mild respiratory depression occur, and the undesired state of narcotization. This is characterized, in part, by minimal responsiveness to stimuli, depressed pharyngeal and laryngeal reflexes, probable airway obstruction, and marked respiratory depression. In managing narcotics, an attempt is made to achieve the former and to avoid the latter. Thus, some respiratory depression is acceptable in order to preserve other clinically desirable agonistic effects.

The potential for prolonged narcotization after anesthesia is related to the narcotic used, its total dosage, and the elapsed time from the last injection. As an illustration, agonistic effects of 0.1 mg fentanyl are apparent for ½ to 1 hour[12] while those of 10 mg morphine average 4 hours.[13] These doses do not produce narcotization. In contrast, the anesthetic dose of fentanyl may easily exceed 0.006 mg/kg (0.42 mg/70 kg); for morphine, 0.5 to 1 mg/kg and more are often used. Anesthetic fentanyl doses produce significant narcotic depression for 4 hours,* while narcotic depression after morphine may range from 4 hours[3] at the lower dose up to 21 hours at the higher dose.[4]

Using fentanyl, we noted (table 2) that the time between the last dose and completion of the operative procedure is important in determining the need for naloxone. Within 45 minutes of the last dose, antagonism

*Harper MH, Hickey RF, Cromwell TH: The magnitude and duration of the effect of fentanyl and Innovar on the ventilatory response to carbon dioxide in man. Presented at the Pulmonary-Respiratory Pharmacology Conference, Davis, California, August 19, 1975

by naloxone is usually required. Beyond an hour, respiratory depression will probably come from other causes. We were unable to show a similar relationship with morphine, but our sample was small, and this requires further study.

The manufacturer of naloxone initially recommended a dose of 0.4 mg IV to counter narcotic depression.[14] Clinicians have varied from this, following a report in 1974 suggesting that naloxone titration permitted better control.[5] To counter fentanyl depression, Heisterkamp and Cohen[5] recommended naloxone increments of 0.1 mg IV every 2 minutes while Petty[15] suggested 1.5 μg naloxone/μg fentanyl IV. Our study used naloxone increments of 1.5 μg/kg IV every 3 minutes until regular respirations exceeded 15/min.

Our regimen and Heisterkamp's may require repeated IV injections of naloxone within the operating room. In addition, Heisterkamp recommends that an additional dose of naloxone equal to half the successful IV dose be given IM 30 minutes later. Our patients did not need a repeat dose after fentanyl (table 4). Differing protocols probably account for the varying regimens. The dose of fentanyl (1.5 ± 0.3 mg) employed by Heisterkamp and Cohen was much higher than Petty's or ours. The prolongation of narcotic action due to the larger dose probably accounts for the supplementary IM recovery room dose of antagonist.

Petty used 0.3 mg of fentanyl for a D & C. Although this dose is less than ours, the duration of this procedure is short. Thus insufficient time for significant excretion of fentanyl required a higher dose of antagonist. We used 0.6 mg of fentanyl to meet clinical requirements, the need for antagonism being related to the time interval from the last dose.

Using morphine, agonistic actions of anesthetic doses may outlast the antagonism of naloxone, inasmuch as the half-life of the former is 207 minutes[4] and that of the latter is but 19 minutes.[16] Clinical suggestions concerning appropriate naloxone dosage have also varied.[3-5,15,17] We used increments of 1.5 μg/kg IV every 3 minutes until regular respirations exceeded 15/min at the completion of operation, and noted a satisfactory postsurgical course in 75 percent of patients (12/16); the remainder required an incremental dose of 1.5 μg/kg naloxone IM in the recovery room. Again, differences in protocol probably account for the varying experiences of others. However, our recommendations stem from the variations in duration of surgery, morphine being injected within 30 minutes of induction.

Narcotics inhibit the respiratory system, raising $Paco_2$, depressing minute ventilation, and depressing responsiveness to CO_2 challenge. However, depression of the respiratory rate is not a consistent finding at usual clinical doses. Eckenhoff[18] reported that 6/21 patients had a decrease in respiratory rate; the remainder either had no change or an increase in rate at a time when the respiratory system was depressed. In contrast, Foldes[19] indicated a consistent decrease in respiratory rate after narcotic supplementation of thiopental-N_2O anesthesia, and narcotic antagonists restored control values.

Heisterkamp and Cohen[5] reported that depression of respiratory rate correlated significantly with depressed minute ventilation and elevated $Paco_2$, yet concluded that rate was a poor criterion for evaluating respiratory adequacy in the individual patient. The postsurgical patient is subject to numerous factors which influence respiratory performance. Stimulation from the wound (not necessarily perceived as pain), awareness, and the antagonistic action of naloxone increase ventilation, while lingering anesthetic, muscle relaxant and narcotic action, binders, immobility, and position decrease ventilation.

Our data indicate that antagonism of the narcotic to the point at which respirations are regular and exceed 15/min in the operating room and 14/min in the recovery room will yield satisfactory ventilation (table 4).

In agreement with other reports,[5,15] we believe that adequate analgesia for the immediate postoperative period can be preserved by judicious titration with naloxone. Only 5/38 patients who received naloxone required additional analgesia in the recovery room (table 5). This confirms the effectiveness of titration, wherein respiratory adequacy can coexist with analgesia.

Vomiting has been reported after naloxone antagonism. Johnstone[4] cited its appearance in 5/6 volunteers, and Longnecker[3] reported 50 episodes after 79 injections of naloxone, used to reverse relatively large morphine doses. Vomiting is a well-known side effect of narcotics and its incidence is accentuated in ambulatory patients. Hasbrouck[20] did not note emesis after naloxone and suggested that incomplete

reversal of the agonist by naloxone may be the cause of vomiting.

We observed 2 episodes of emesis in 38 patients given naloxone, but 1/20 patients not receiving naloxone also vomited. Therefore, it appeared that naloxone did not increase the incidence of emesis. However, droperidol, a potent antiemetic, was included in the anesthetic management and this may have contributed to the lessened incidence.[21]

Our study suggests that titration of naloxone affords safety and comfort in the early postsurgical period after narcotic-supplemented anesthesia.

REFERENCES

1. Lowenstein E, Hallowell P, Levine FH, et al: Cardiovascular response to large doses of intravenous morphine in man. N Engl J Med 281:1389-1393, 1969

2. Walts LF, Levin N, Dillon JB: Assessment of recovery from curare. JAMA 213:1894-1896, 1970

3. Longnecker DE, Grazis PA, Eggers GWN Jr: Naloxone for antagonism of morphine-induced respiratory depression. Anesth Analg 52:447-453, 1973

4. Johnstone RE, Jobes DR, Kennell EM, et al: Reversal of morphine anesthesia with naloxone. Anesthesiology 41:361-367, 1974

5. Heisterkamp DV, Cohen PJ: The use of naloxone to antagonize large doses of opiates administered during nitrous oxide anesthesia. Anesth Analg 53:12-18, 1974

6. Romagnoli A: Duration of action of fentanyl. Anesthesiology 39:568-569, 1973

7. Evans LEJ, Roscoe P, Swainson CP, et al: Treatment of drug overdosage with naloxine, a specific narcotic antagonist. Lancet 3:452-455, 1973

8. Kallos T, Hudson HE, Rouge JC, et al: Interaction of the effects of naloxone and oxymorphone on human respiration. Anesthesiology 36:278-285, 1972

9. Kallos T, Smith TC: Naloxone reversal of pentazocine-induced respiratory depression. JAMA 204:932, 1968

10. Kersh ES: Treatment of propoxyphene overdosage with naloxone. Chest 63:112-114, 1973

11. Blumberg H, Dayton HB, Wolf PS: Counteraction of narcotic antagonist analgesics by the narcotic antagonist naloxone. Proc Soc Exp Biol Med 123:755-758, 1966

12. Corssen G, DeKornfeld TJ: Comparison of the respiratory depressant effects of fentanyl, fentanyl and dehydrobenzperidol, and morphine. Anesthesiology 27:213-214, 1966

13. Jaffe JH: Narcotic analgesics. The Pharmacologic Basis of Therapeutics. Edited by LS Goodman, A Gilman. New York, The Macmillan Company, 1965, chapter 15, p 258

14. Endo Laboratories, Inc: The first essentially pure narcotic antagonist Narcan (naloxone HCl). November 1973

15. Petty WC: Duration of action of naloxone. Madrid, Spain, Proceedings of the IV European Congress of Anesthesiology, September 1974, #298, p 132

16. Kosterlitz HW, Watt AJ: Kinetic parameters of narcotic agonists and antagonists, with particular reference to N-allylnoroxymorphone (naloxone). Br J Pharmac Chemother 33:266-276, 1968

17. Evans JM, Hogg MIJ, Lunn JN, et al: Degree and duration of reversal by naloxone of effects of morphine in conscious subject. Br Med J 2:589-591, 1974

18. Eckenhoff JE, Helrich M, Hege MJD, et al: Respiratory hazards of opiates and other narcotic analgesics. Surg Gynecol Obstet 101:701-708, 1955

19. Foldes FF, Schapira M, Torda TAG, et al: Studies on the specificity of narcotic antagonists. Anesthesiology 26:320-328, 1965

20. Hasbrouck JD: Guest discussion to Longnecker DE, Grazis PA, Eggers GWN Jr: Naloxone for antagonism of morphine-induced respiratory depression. Anesth Analg 52:447-452, 1973

21. Patton CM, Moon MR, Dannemiller FJ: The prophylactic antiemetic effect of droperidol. Anesth Analg 53:361-364, 1974

Enflurane as a Primary Anesthetic Agent for Patients with Chronic Obstructive Pulmonary Disease

RENE RODRIGUEZ, MD*
MARTIN I. GOLD, MD†
Miami, Florida‡

For years, halothane has been the anesthetic agent of choice for patients with chronic obstructive pulmonary disease (COPD) and reversible airway disease (asthma). Enflurane was compared with halothane in 100 patients with COPD substantiated by spirometry and history. Intraoperative and postoperative complications in each relatively homogeneous 50-patient group were assessed. Spirometry, blood gases, chest x-rays, incidence of complications involving secretions, coughing, wheezing, and cardiovascular problems were similar in both groups. Enflurane appears to be equivalent to halothane as an anesthetic in such patients.

HALOTHANE has long been found useful for the anesthetic management of patients with chronic obstructive pulmonary disease (COPD) and reversible airway disease (asthma).[1] Enflurane also has been reported clinically successful in patients with COPD.[2] The purpose of this investigation was to compare these 2 agents as the primary agent for such patients.

METHOD

After informed consent, patients with a "chart diagnosis" of COPD for both elective and daytime emergency operations were spirometrically screened. The vital capacity (VC) and 1-second forced expiratory volume (FEV_1) were measured at the bedside§ 3 times in all patients. Patients with an $FEV_1 < 70\%$ of VC, were admitted to the study.[3] Arterial blood gases were measured before operation ($F_{IO_2} = 0.21$). Odd-aged patients received halothane and even-aged patients received enflurane.

Patients were premedicated with 2.5 mg/kg of pentobarbital and/or 0.10 mg/kg of morphine sulfate plus 0.5 mg of atropine. In the operating theater, a blood-pressure cuff and ECG leads were applied and IV infusion started, followed by thiopental induction and the primary anesthetic, enflurane or halothane, plus a 50 percent mixture of N_2O-O_2 ($F_{IO_2} = 0.5$). All patients were intubated with the aid of succinylcholine and most were ventilated with a mechanical ventilator; pancuronium was used as the primary relaxant.

Tidal volumes and F_{IO_2} were measured with a Wright respirometer and a Beckman O_2 analyzer, respectively. One investigator (RR) performed the spirometry, withdrew arterial blood for gas analysis, and monitored each patient; he and the anesthetist assigned to this patient made independent judgments concerning the anesthesia, noting all complications and other useful data.

After operation, each patient was extubated and transferred to the postoperative

§McKesson Vitalor calibrated with a water spirometer.

*Research Fellow.

†Professor, Department of Anesthesiology.

‡University of Miami School of Medicine; Anesthesia Service, Veteran's Administration Hospital, Miami, Florida 33125.

Reprints to Dr. Gold.

Paper received: 7/24/75
Accepted for publication: 2/11/76

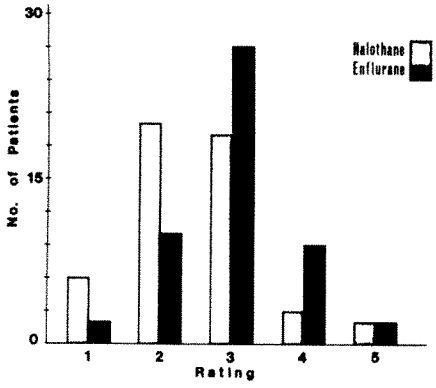


FIG 1. ASA Rating.

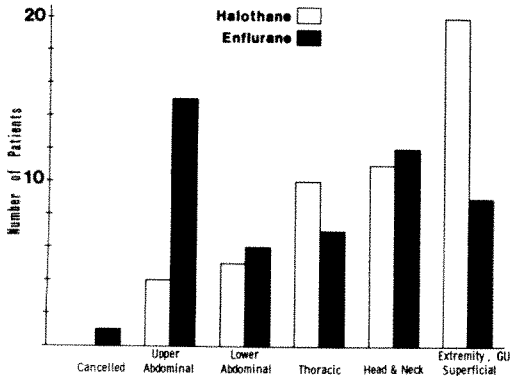


FIG 2. Type of Surgery.

recovery room (PAR), inhaling O_2 through a nasal cannula ($FIO_2 = 0.3$). After leaving the PAR, he went to the surgical intensive care unit or ward, where he was under observation until hospital release. Statistical analysis was by computer.*

RESULTS

Figures 1 and 2 and tables 1 and 2 show preoperative data and types of operation. Duration of anesthesia (mean 3 hours) and mean dosage of thiopental and pancuronium were similar in both groups, as were tidal volumes and respiratory rates, which averaged 800 ml and 12/min, respectively. Blood gases (fig 3), analyzed preoperatively, intraoperatively, and postoperatively, showed no significant differences between groups.

Intraoperative complications (fig 4) included troublesome wheezing, coughing of more than 2 minutes duration, difficulty in managing secretions, and cardiovascular problems; no significant differences (chi^2 test) were seen between the 2 groups. Hypotension was defined as a persistent (more than 1 min) decrease of 33 percent in systolic blood pressure. Pulse rates <60 or >120 were defined as bradycardia or tachycardia, respectively. Arrhythmias were considered significant if >1 minute in duration. They were primarily atrial in origin, with some premature ventricular contractions.

Nine patients wheezed before receiving enflurane; wheezing disappeared intraoperatively in 5. No patient in the halothane group wheezed preoperatively. No clinical evidence of severe bronchospasm occurred in

*Univac Data 100.

TABLE 1
Preoperative Patient Characteristics

	Agent	Mean ± SD	Range	
			Minimum	Maximum
Age, yr	E	56 ± 10	40	83
	H	54 ± 10	25	77
Height, cm	E	177 ± 8	150	193
	H	177 ± 10	147	187
Weight, kg	E	72 ± 17	48	112
	H	72 ± 13	51	104
Vital capacity, L	E	3.0 ± 0.7	1.7	4.5
	H	3.2 ± 0.7	1.0	4.8
FEV_1, L/sec	E	1.78 ± 0.54 (58%)	0.75	3.17
	H	1.86 ± 0.67 (53%)	0.67	5.04

E = enflurane (50 patients).
H = halothane (50 patients).

TABLE 2
History of COPD, Number of Patients

History of COPD	Years	0-5	5-15	15+
	E	11	27	12
	H	5	38	7
Smoking	Packs/day	0	1	1-2	2+
	E	3	7	22	18
	H	1	4	15	30
Sputum	Cups/day	<1	1	>1
	E	19	27	4
	H	16	33	1
Cough	Severity	None	No trouble	Trouble
	E	4	21	25
	H	4	18	28

E = enflurane (50 patients).
H = halothane (50 patients)

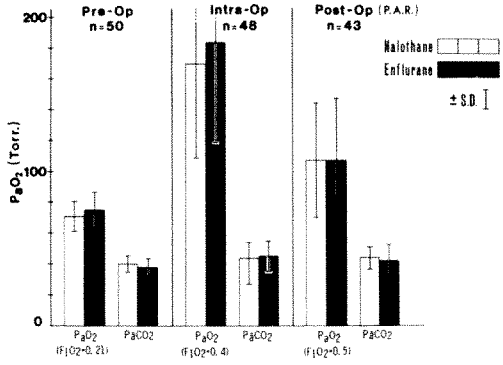


FIG 3. Blood Gas Data.

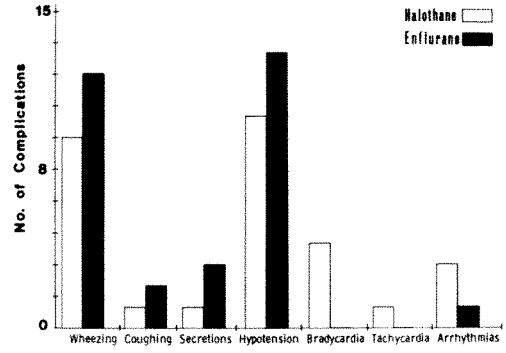


FIG 4. Intraoperative Complications.

any patient. One patient developed severe hypotension; operation was postponed until after treatment for hypovolemia, when he received enflurane without sequelae.

After leaving the PAR, of those who received halothane, 12 (24%) developed pneumonia, 6 ((12%) atelectasis, and 5 (10%) pleural effusion. Of those who received enflurane, 8 (16%) developed pneumonia, 7 (14%) atelectasis, and 7 (14%) pleural effusion.

DISCUSSION

This investigation involved patients with COPD defined by spirometry and history, not merely a "chart diagnosis." While demographic data reflect relative homogeneity between the 2 groups, a few more patients with upper abdominal surgery and less with extremity and superficial operations received enflurane, and the mean ASA physical rating was slightly lower in the halothane patients. Therefore, more "worse-risk" patients and some for more complicated surgery were maintained on enflurane. However, this skewing does not affect the validity of the comparison.

Enflurane and halothane intraoperative blood gases were basically similar, as was the clinical incidence of wheezing, troublesome coughing, and secretions, all potentially dangerous in this type of patient. Hypotension was frequent but, again, the incidence was similar in both groups. Both of these liberally halogenated anesthetic agents carry this stigma, especially in poor-risk patients.[4-7] Bradycardia, tachycardia, and persistent arrhythmias occurred rarely and with similar incidence in both groups. Halothane was associated with more arrhythmias than enflurane ($p<0.05$), while enflurane was associated with more frequent hypotension ($p<0.05$).

No patient was considered to have been hypoxemic, although a few isolated Pao_2s were lower than one would have expected from the associated FIO_2 and estimated PAO_2. COPD is associated with an increased incidence of respiratory complications, decreased Pao_2, and hypotension. Decreased cardiac output plus a higher $PA\text{-}ao_2$ difference was not unexpected.[8-11]

In the PAR, blood gases in both groups were similar. Each patient had been extubated and was receiving an FIO_2 estimated to have been 0.25 to 0.3 (40% O_2 was delivered to the nasal cannula; as this was diluted by a variable amount of air, FIO_2 could only be estimated). Postoperative wheezing and late postoperative respiratory complications in both groups were virtually identical (average of 3 postoperative chest

x-rays). Twelve (24%) halothane and 8 (16%) enflurane patients developed pneumonia ($p<0.05$); however, the site and duration of operation are interdependent variables related to incidence of respiratory complications and were not analyzed because of low sample numbers.

Patients with COPD must be considered far more of a risk than normal patients, and complications may arise either during or after anesthesia for reasons that are not clear.[8-12] There is decreased ciliary activity, especially in smokers;[13] there is also an increase in secretions. Such patients rely on the cough mechanism to bring up secretions and foreign material. During anesthesia, the cough reflex is significantly diminished, as is patient response to CO_2.[8] Patients with COPD have an exaggerated depression of CO_2 response unrelated to the operative procedure or anesthesia. Therefore it is not surprising that these patients have an increased incidence of intraoperative and postoperative respiratory complications.[8-12] Halothane, a beta-adrenergic stimulating agent,[14] has been clinically successful in such patients, probably because it is also a mild bronchodilator, is not as irritating as other inhalation agents, and is not associated with a significant amount of secretions.[15,16] A second anesthetic agent for patients with COPD with similar characteristics would be a welcome addition in the anesthesiologist's quest to avoid morbidity in these patients.

The interdependent influences of many variables reflect the limitations of such a 2-drug investigation as reported here. Nevertheless, the objective and clinical evidence presented in these 100 patients, within the limitations of the protocol, leads us to suggest that enflurane be ranked equally with halothane for anesthesia in patients with COPD.

REFERENCES

1. Colgan FJ: Performance of lungs and bronchi during inhalation anesthesia. Anesthesiology 26: 778-785, 1965

2. Dobkin AB, Heinrich RG, Israel JS, et al: Clinical and laboratory evaluation of a new inhalation agent: compound 347. Anesthesiology 29:275-287, 1968

3. Comroe JH Jr, Forster RE II, Dubois AB, et al: The Lung, Clinical Physiology and Pulmonary Function Tests. Second edition. Chicago, Year Book Medical Publishers, Inc, 1962

4. Gold MI: Anesthesia for the asthmatic patient. Anesth Analg 49:881-888, 1970

5. Lebowitz MH, Blitt CD, Dillon JB: Clinical investigation of compound 347 (Ethrane). Anesth Analg 49:1-10, 1970

6. Marshall BE, Cohen PJ, Klingenmaier CH, et al: Some pulmonary and cardiovascular effects of enflurane anaesthesia with varying $Paco_2$ in man. Br J Anaesth 43:996-1002, 1971

7. Price HL, Price ML: Has halothane a predominant circulatory action? Anesthesiology 27: 764-769, 1966

8. Pietak S, Weenig CS, Hickey RF, et al: Anesthetic effects on ventilation in patients with chronic obstructive pulmonary disease. Anesthesiology 42:160-166, 1975

9. Gaensler EA, Weisel RD: The risks in abdominal and thoracic surgery in COPD. Postgrad Med 54:183-192, 1973

10. Philbin DM, Sullivan SF, Bowman FO, et al: Postoperative hypoxemia: contribution of the cardiac output. Anesthesiology 32:136-142, 1970

11. Tarhan S, Moffitt EA, Sessler AD, et al: Risk of anesthesia and surgery in patients with chronic bronchitis and chronic obstructive pulmonary disease. Surgery 74:720-726, 1973

12. Marshall BE, Wyche MQ Jr: Hypoxemia during and after anesthesia. Anesthesiology 37:178-209, 1972

13. Lichtiger M, Landa JF, Hirsh JA: Velocity of tracheal mucus in anesthetized women undergoing gynecologic surgery. Anesthesiology 42:753-756, 1975

14. Klide AM, Aviado DM: Mechanism for the reduction in pulmonary resistance induced by halothane. J Pharmacol Exp Ther 158:28-35, 1967

15. Hickey RF, Graf PD, Nadel JA, et al: The effects of halothane and cyclopropane on total pulmonary resistance in the dog. Anesthesiology 31:334-343, 1969

16. Fletcher SW, Flacke W, Alper MH: The actions of general anesthetics on tracheal smooth muscle. Anesthesiology 29:517-522, 1968

Unexpected Hepatic Dysfunction Found by Multiple Laboratory Screening

WILLIAM H. SCHEMEL, MD*

During a 1-year period, 7620 elective surgical admissions were given multiple laboratory screening (SMA-18) determinations. Of these, 11 healthy patients, aged 10 to 54, with a pretest classification of ASA 1 (no systemic disease) were found to have clearly abnormal elevations of the SGOT, SGPT, and LDH levels. The proposed elective surgical procedures and anesthesia were canceled. All 11 patients proved to have overt liver pathology by further testing, and 3 later became clinically jaundiced. No cases of unexplained postsurgical jaundice occurred in any of the other 7609 operated cases during the 1-year study. The incidence of clearly elevated enzyme levels in voluntary hospital surgical admissions is approximately 1/700 and the incidence of clinical jaundice is approximately 1/2540. There appears to be a seasonal variation, with the preponderance of elevated enzyme levels in the winter and spring months.

THE toxicity of halogenated anesthetics remains a frustrating and controversial subject, primarily due to lack of necessary information. Carney and Van Dyke[1] reported the incidence of hepatitis following halothane anesthesia to be approximately 1/2500, and mortality from post-halothane hepatitis is reportedly somewhere between 1/9000 and 1/40,000.[2] The need has existed for a prospective study to determine the incidence of undiagnosed hepatitis in the general population, which might become clinically evident after surgical anesthesia. The purpose of the present study was to determine the incidence of hepatic dysfunction in patients admitted for elective surgery, with relation to 1 year's experience with preoperative SMA-18 multiple laboratory screening.

METHOD

Our institution is a 550-bed voluntary general hospital with mostly private patients. During the period July 1, 1974, to June 30, 1975, a total of 7620 patients admitted for elective surgery were studied. Blood for SMA-18 determination was drawn the afternoon of admission on the day before operation, with the report in the chart preoperatively. The SMA-18 determines SGOT, SGPT, LDH, alkaline phosphatase, total bilirubin, creatinine, uric acid, cholesterol, inorganic phosphorus, K^+, Na^+, Ca^{++}, Cl^-, albumin, total protein, glucose, BUN, and CO_2.[3]

While all these have proved of value in the diagnosis, treatment, and anesthetic management of individual cases, the enzyme determinations (SGOT, SGPT, and LDH) have been of critical importance, especially concerning the determination of hepatic dysfunction.

The range of normal values (± 2 SDM) accepted in this laboratory are:

SGOT	7 to 40 mU/ml
SGPT	7 to 40 mU/ml
LDH	100 to 225 mU/ml

The normal range is based on the statistical concept of the normal distribution of the Gaussian curve. It has been shown that 66 percent of the population fall within 1 SD and 95 percent within 2 SDs.[4] Many

*Attending Anesthesiologist, Sisters of Charity Hospital, Buffalo; Clinical Assistant Professor, Department of Anesthesiology, State University of New York, Buffalo, New York 14214.

Paper received: 11/10/75
Accepted for publication: 2/17/76

factors, as well as disease processes, can produce slight, transient elevations of these enzymes; these are of no real consequence.[5] As a "rule of thumb," the values may be considered clearly abnormal only when they are more than twice the upper limit of normal.

DISCUSSION

As all 11 patients had clearly abnormal enzyme levels, the proposed operations were canceled. The tests were repeated and in all cases were again clearly abnormal. At this point, the patients were again interviewed (the routine history having been taken and physical examination made on admission) and questioned regarding symptoms related to hepatic function. None of the patients had any of the usual symptoms related to hepatic disease. Some were indignant at having their proposed surgical procedures canceled. All were referred to their primary physician for further diagnosis and treatment and all were diagnosed as having definite liver disease on the basis of further laboratory testing or pathology reports of liver biopsies. Three developed clinical jaundice. During the period when enzymes were elevated, most patients experienced no symptoms; a few had some minor complaints, such as tiredness and loss of appetite. The course of the disease in the 3 patients with jaundice was benign, with apparent complete recovery.

The incidence of clearly elevated enzymes in this group was approximately 1/700 and the incidence of clinical jaundice was 1/2540. During the first 6 months of the study, only 1 patient was found with clearly abnormal enzyme elevations; the other 10 were found between January and June.

The results of this 1-year's experience revealed a number of significant findings and raised some questions. The 11 patients reported here, all ASA status I, would have undergone elective surgical procedures had they not been found to have elevated enzyme levels preoperatively. At least 3 of them would have developed jaundice in the postoperative period. Would the diagnoses of viral hepatitis, subsiding viral hepatitis, and infectious mononucleosis have been different had they received halogenated anesthetics? Would the normal course of hepatic disease have been altered by anesthesia and surgery? At this point, it is interesting to note that there have been no reported cases of unexplained postoperative jaundice in this hospital since the advent of multiple laboratory screening.

When the enzyme levels are clearly abnormal, it is best to postpone surgery until the reason for the elevation has been determined. When the enzyme levels are slightly elevated, it is difficult to determine the proper course of action. In these instances, it has been our policy either to use regional technics or, if inhalation anesthesia is required, to avoid the use of halogenated compounds.

TABLE
"Healthy" Surgical Admissions with Elevated SGOT, SGPT and LDH Tests
(All Patients ASA Status I)

Patient	Age	Sex	Operation proposed	Post-test diagnosis	Became jaundiced
1	10	M	Scalp wen	Infectious mononucleosis	No
2	47	F	Hysterectomy	Viral hepatitis*	Yes
3	24	F	Laparoscopy	Viral hepatitis*	No
4	54	F	D & C	Cirrhosis	No
5	23	F	Laparoscopy	Infectious mononucleosis	Yes
6	21	M	Inguinal hernia	Acute alcohol hepatitis*	No
7	23	M	Menisectomy	Chronic hepatitis	No
8	35	M	Skin graft	Early cirrhosis	No
9	16	F	Breast biopsy	Viral hepatitis	Yes
10	26	M	Laminectomy	Alcoholic hepatitis	No
11	25	M	Dental extractions	Hepatic dysfunction (industrial toxin?)*	No

*Liver biopsy.

Several other patients with known systemic disease (ASA II or greater) also had their elective surgical procedures postponed or canceled by their primary physician as a result of these tests, but they are not included in this report.

The incidence of postoperative hepatitis reported by Carney (1/2525) is nearly identical with the incidence of clinical jaundice in our preoperative studies (1/2540). A similar report from another institution in this community[6] revealed almost identical results, 1/2180 jaundiced and 1/727 elevated enzymes. Their seasonal distribution also was similar to ours.

CONCLUSIONS

From these data, we conclude that it is possible that many cases which have been diagnosed as halothane hepatitis could well have been infectious hepatitis becoming clinically evident after surgical procedures. From the incidence of undetected hepatic dysfunction in ASA I patients admitted for elective surgery, obviously many thousands of such patients have been anesthetized over the years by a variety of technics and have remained asymptomatic.

It is our recommendation that multiple laboratory screening, including SGOT, SGPT, and LDH, be done routinely on admission, to identify those patients in the general population who might need further evaluation, therapy, and observation before elective surgery.

REFERENCES

1. Carney FMT, Van Dyke RA: Halothane hepatitis: a critical review. Anesth Analg 51:135-160, 1972

2. Summary of the National Halothane Study: Possible association between halothane anesthesia and postoperative hepatic necrosis. JAMA 197:775-788, 1966

3. Benson ES, Strondjord PE: Multiple laboratory screening. New York, Academic Press, Inc, 1969, pp 181-194

4. Preston JA, Troxel DB: Biochemical profiling in diagnostic medicine. Technicon Instruments Corp. 1:2, 1971

5. Preston JA, Troxel DB: Biochemical profiling in diagnostic medicine. Technicon Instruments Corp. 2:1-50, 1974

6. Wataneeyawech M, Kelly KA Jr: Hepatic diseases: unsuspected before surgery. NY State J Med 75:1278-1281, 1975

HYPERTENSION. Postoperative hypertension may occur in nearly one-third of patients following aorta-coronary bypass graft operations. In addition to increasing the risk of hemorrhage the hypertension may increase myocardial oxygen requirements. Seven of 12 patients investigated by the authors became hypertensive (blood pressure >140/90) after myocardial revascularization. Systemic vascular resistance was greater in hypertensive as compared with normotensive patients while heart rates and cardiac outputs were similar. Thoracic epidural anesthesia administered to the hypertensive patients reduced systolic blood pressure to an average of 105 torr and improved the diastolic pressure-time index/systolic pressure-time index ratio (an indirect measurement of subendocardial oxygenation). In addition to the pharmacologic sympathectomy epidural anesthesia has the added advantage of analgesia. *(Hoar PF, Hickey RF, Ullyot DJ: Systemic hypertension following myocardial revascularization. A method of treatment using epidural anesthesia. J Thorac Cardiovas Surg 71:859-864, 1976)*

Postpartum Hypertension and Convulsion After Oxytocic Drugs

EZZAT ABOULEISH, MB, BCh, MD*

An 18-year-old primipara developed acute hypertension leading to cerebral edema and convulsions following the IV injection of a bolus of 10 units of oxytocin with 0.2 mg methylergonovine maleate. Oxytocin in a dose of more than 2 units should not be administered IV in a single injection, as severe hypotension may result. If oxytocin is required, it can be injected either IM, or by IV pump or drip. The use of ergot in obstetrics should be limited to the treatment of life-threatening postpartum hemorrhage and be given only by the IM route. Ergot should not be administered to patients with cardiac, renal, or hypertensive disease, or in association with a vasoconstrictor.

DESPITE the documented potential danger of administering oxytocin and/or methylergonovine maleate intravenously in a bolus,[1-9] this procedure is still used by some physicians. The present report is intended to remind the anesthesiologist of the hazards of this therapy.

CASE REPORT

An 18-year-old gravida 1, para 0, was admitted to the hospital at 0100 hrs on her expected date of confinement. Her antepartum course was uneventful, total weight gain was 10.9 kg, and average blood pressure was 110/70. On admission, she was apprehensive, with a blood pressure of 140/100, reflexes were brisk, and the cervix was 7 cm dilated with vertex presentation. Hemoglobin was 13.2 gm/100 ml, there was no edema, and urine was negative for albumin and dextrose. After IM injection of 50 mg of phenothiazine and 50 mg of meperidine, the blood pressure decreasd to 110/70 and reflexes became normal. Labor progressed satisfactorily, and, in about 2 hours, the patient was ready for delivery.

At 0305 hrs, subarachnoid block to T-10 was achieved without difficulty, using 50 mg of lidocaine through a 26-gauge spinal needle. Blood pressure was stable at 110/65, and no vasopressor was administered. At 0316, a female baby weighing 3520 gm was delivered (Apgar 9-10). At 0318, the placenta spontaneously separated and was delivered. Immediately afterward, 10 units of oxytocin and 0.2 mg of methylergonovine maleate were injected in a single IV dose, and 10 units of oxytocin in 5 percent dextrose in water (D/W) were administered in a continuous IV drip.

At 0335, the blood pressure increased to 140/100. In the recovery room, at 0345, blood pressure reached 200/130 and the patient complained of severe headache. There was no edema and reflexes were normal. The IV injection of 5 mg of diazepam and the IM injection of 15 mg of morphine failed to lower the blood pressure or relieve the headache, and the patient became nauseated and began vomiting. Bladder catheterization revealed 1100 ml of clear urine, followed by a urine output of 100 ml/hr. There was no proteinuria. At 0430, an IM injection of 120 mg of phenobarbital was followed by sedation and decrease in blood pressure, which was maintained around 160/100.

At 0855, the patient became incoherent, with body tremors, followed by generalized rigidity and a grand mal seizure. Phenobarbital (100 mg) was injected IV, O_2 was administered, and the seizure stopped without recurrence. Examination of the eye fundi showed constricted blood vessels without hemorrhage or exudates, and neurologic examination showed no signs of localization. Lumbar puncture with a 20-gauge spinal

*Associate Professor of Clinical Anesthesiology, University of Pittsburgh School of Medicine; Director of Obstetric Anesthesia, Magee-Womens Hospital, Pittsburgh, Pennsylvania 15213.

Paper received: 6/30/75
Accepted for publication: 3/1/76

needle showed clear CSF with grossly elevated pressure. Actual measurement of the pressure was not possible because of the patient's lack of cooperation. The urine output, after temporary reduction to 20 ml/hr for 2 hours, rapidly increased to preseizure level (100 ml/hr). Albuminuria and hematuria were present only during the oliguric period.

Blood examination showed WBC 10,000, hemoglobin 12.7 gm/100, platelets 150,000, fibrinogen 341 mg/100 ml, prothrombin time 12 sec, partial thromboplastin time 34 sec, plasma thrombin time 26 sec, urine/serum osmolality 602/282 mOsm/kg water, Na^+ 137 mEq/L, K^+ 4.7 mEq/L, Cl^- 105 mEq/L, BUN 13 mg/100 ml, and creatinine 0.5 mg/100 ml.

Fluid intake in the first 24 hours was 1 L of 5 percent D/W plus 1.5 L of 5 percent dextrose with 0.2 percent NaCl. The patient was maintained on injection of phenobarbital, 60 mg IM every 8 hours and diphenylhydantoin, 100 mg IM every 12 hours. Her body temperature remained normal and her consciousness rapidly improved 24 hours after delivery. Thereafter, blood pressure remained around 110/70, her stay in the hospital was uneventful, and on the 8th postpartum day she and her baby were discharged in good condition.

DISCUSSION

Oxytocic drugs have a significant effect on the cardiovascular system. Oxytocin causes vasodilation of both alpha- and beta-adrenoreceptive blood vessels.[8] The action occurs in less than 30 seconds and is maintained for 3 to 5 minutes.[7] The vasodilating effect of oxytocin causes transient hypotension, the degree and duration of which are proportionate to the dose of the drug and the rate of injection. The average drop in blood pressure after oxytocin injection (0.1 unit/kg) in the form of an IV bolus is 45 percent.[9] Hypotension due to oxytocin is minimized by the lithotomy position.[8] However, such hypotension becomes especially dangerous in a hypovolemic patient in whom vasoconstriction is an important factor in maintaining the blood pressure.

Five to 10 seconds after the onset of hypotension, tachycardia occurs, with an average increase in heart rate of 20 beats/min.[9] The tachycardia, which is reflex in origin and secondary to the hypotension, is associated with S-T segment depression and T wave inversion, denoting myocardial ischemia. This is due to coronary insufficiency as a result of hypotension, combined with increased O_2 demand secondary to the tachycardia.[2,8,10] There is also mild myocardial depression, manifested by antiarrhythmic properties of oxytocin.[11] Such mild myocardial depression becomes significant in a patient with cardiac disease.

Therefore, if oxytocin is required, it can be injected either IM, or by IV pump or drip; it should not be administered by IV bolus in a dose exceeding 2 units.

Ergot preparations, in contrast to oxytocin, are known to cause vasoconstriction.[12] The vasoconstrictive action of ergonovine is less than that of other ergot alkaloids, and methylation further reduces its vasoconstrictive effects. A pressor effect has been seen in about 48 percent of patients following ergonovine administration and in 22 percent after methylergonovine.[4] The incidence of severe hypertension (systolic elevation of >25 torr and diastolic of >20 torr) was reported in 2 percent of cases following IV injection of methylergonovine and in 4.6 percent with concomitant administration of vasopressor.

Hypertension also can follow the IM injection of ergot alkaloids.[3] Vasoconstriction, through a direct stimulation of blood vessels both at the arterial and venous sides,[13] leads to increased peripheral resistance and rise of both arterial blood pressure and central venous pressure. Ergot also has a depressant effect on the vasomotor center, preventing compensatory vasodilation secondary to afferent impulses from the baroreceptors. The increased venous return to the heart following relief of the inferior vena caval compression after delivery and the diminution of the vascular bed following tetanic contraction of the uterus potentiate the postpartum rise of blood pressure. The vasoconstrictive effect of ergot becomes manifest in 3 minutes and lasts for several hours.[8]

Blood pressure elevation following ergot preparations is particularly pronounced in toxemias of pregnancy, hypertension, presence of hypoxia, administration of vasopressors,[3] or marked apprehension.[5] In our case report, toxemia was excluded, the high blood pressure and hyper-reflexia encountered on admission probably being due to apprehension, since blood pressure and reflexes became normal following phenothiazine and meperidine administration.

Since the incidence of a dangerous rise of blood pressure after administration of ergot alkaloids is rare and hypertension would otherwise be attributed to postpartum toxemia, some obstetricians continue to give ergot IV. However, this is particularly dangerous in patients with cardiovascular disease, hypertension, respiratory disease, renal disease, or chronic anemia. Sudden hypertension produced by ergot causes a strain on the heart and may be associated with coronary vasoconstriction, leading to myocardial ischemia, acute heart failure, and acute pulmonary edema. It may also lead to cerebral edema, as in the case reported, or even to cerebral hemorrhage.[3] Retinal detachment following IV injection of 0.2 mg methylergonovine and 5 units oxytocin also has been described;[6] the mechanism was thought to be spasm of the choroidal vessels, producing an increase in choroidal hydrostatic pressure and transudation of fluid into the subretinal space.

If ergot is administered during general anesthesia under such potent drugs as halothane, or during regional analgesia, its vasoconstrictive action may be counteracted by the vasodilative effect of these technics. Thus, the hypertensive effect of ergot may be masked and the lungs and brain may be temporarily protected from edema or hemorrhage until the vasodilation wears off.

To treat the hypertensive episode produced by ergot, slow IV injection of 12.5 to 15 mg of chlorpromazine is recommended. Hydralazine infusion has also been effective, since it causes generalized vasodilation, particularly of the renal vessels.[14]

Although pharmaceutic literature[15] suggested that methylergonovine maleate might be slowly injected IV over a period of no less than 60 seconds while monitoring the blood pressure this is not safe enough in view of the delay (3 min) in evidence of the hypertensive response.[8] Therefore, if ergot is to be used, it should be administered by IM route for a life-threatening uterine atony resistant to oxytocin.

Since the vasoconstrictive effect of ergot is opposite to the vasodilative action of oxytocin, this may lead to the erroneous assumption that, by simultaneous IV administration of both drugs, the effect of one will nullify that of the other. However, onset and duration of action of the 2 drugs are so different that the patient is exposed to the harmful effects of both.

ACKNOWLEDGMENT

My appreciation extends to Dr. Eberhard Mueller-Heubach for his advice and to Miss Lois Sprague and Miss Kathy Kutzavitch for secretarial help.

REFERENCES

1. Woodbury RA, Hamilton WF, Volpitto PP, et al: Cardiac and blood pressure effects of Pitocin (oxytocin) in man. J Pharmacol Exp Ther 81:95-100, 1944

2. Bergquist JR, Kaiser IH: Cardiovascular effects of intravenous syntocinon. Obstet Gynecol 13:360-364, 1959

3. Casady GM, Moore DC, Bridenbaugh DL: Postpartum hypertension after use of vasoconstrictor and oxytocic drugs. JAMA 172:101-105, 1960

4. Ringrose CAD: The obstetrical use of ergot: a violation of the doctrine "Primum non nocere." Can Med Assoc J 87:712-714, 1962

5. Baillie TW: Vasopressor activity of ergometrine maleate in anaesthetized parturient women. Br Med J 1:585-588, 1963

6. Gombos GM, Howitt D, Chem S: Bilateral retinal detachment occurring in the immediate postpartum period after methylergonovine and oxytocin administration. Eye Ear Nose Throat Mon 48: 680-682, 1969

7. Hendricks CH, Brenner WE: Cardiovascular effects of oxytocic drugs used postpartum. Am J Obstet Gynecol 108:751-760, 1970

8. Johnstone M: The cardiovascular effects of oxytocic drugs. Br J Anaesth 44:826-834, 1972

9. Weis FR, Peak J: Effects of oxytocin on blood pressure during anesthesia. Anesthesiology 40:189-190, 1974

10. Mayes BT, Shearman RP: Experience with synthetic oxytocin—the effects on cardiovascular system and its use for the induction of labour and control of the third stage. J Obstet Gynaecol Br Commonw 63:812-818, 1956

11. Katz RL: Antiarrhythmic and cardiovascular effects of synthetic oxytocin. Anesthesiology 25: 653-661, 1964

12. Goodman LS, Gilman A: The Pharmacological Basis of Therapeutics. Fifth edition. New York, The Macmillan Company, 1975, pp 540-541

13. Brooke OG, Robinson BF: Effect of ergotamine and ergometrine on forearm venous compliance in man. Br Med J 1:139-142, 1970

14. Browning DJ: Serious side effects of ergometrine and its use in routine obstetric practice. Med J Aust 1:957-959, 1974

15. Physicians' Desk Reference (PDR). 30th edition. Oradell, New Jersey, Medical Economics Company, 1976, p 1348

A Simple Technic to Minimize Tracheal Aspiration

ROY F. CUCCHIARA, MD*

THE safe induction of general anesthesia for emergency surgery in a patient with a full stomach can be challenging to even the most experienced clinician. The presence of ileus, bowel obstruction, or gastric-outlet obstruction may place the gastric contents under greater than normal pressure. Regurgitation under such circumstances may be so voluminous as to overwhelm the awake debilitated patient and cause him to aspirate a significant quantity of gastric contents. The volume of such gastric contents may exceed the capacity of available suction apparatus.

Anesthesiologists have proposed various devices,[1] positions,[2] and technics, such as cricoid pressure,[3] the "crash induction,"[4] the awake intubation,[5] and use of a clear anesthesia mask, to help prevent catastrophic regurgitation. This report adds a simple, but apparently not widely known, adjunct. The case is representative of five in which the technic has been employed effectively.

CASE REPORT

This patient was a slender 68-year-old woman with signs and symptoms of acute small-bowel obstruction, believed to be secondary to peritoneal adhesions from a previous hemicolectomy. A trial of medical management with a Miller-Abbott tube had been unsuccessful. With a nasogastric tube in place, her respiratory rate was 32/min and shallow. Except for a markedly distended abdomen, physical examination was unremarkable. Laboratory and electrolyte values were within normal limits and she was not significantly dehydrated.

A rapid induction was planned. The nasogastric tube was suctioned, irrigated, and intermittently suctioned as it was withdrawn, with no return of gastric contents. After administration of 3 mg of d-tubocurarine, the patient was preoxygenated for 3 minutes. With cricoid pressure applied, she was then given 2 mg/kg of sodium thiopental, followed immediately by 2 mg/kg of succinylcholine. The mask was removed and the laryngoscope inserted for intubation. With no visible signs of movement, the patient promptly regurgitated sufficient quantities of gastric material to overwhelm the capacity of the suction apparatus. Gastric material ran out of her mouth and completely obscured the view into the pharynx.

The endotracheal tube was immediately inserted into the esophagus with the realization that no view of the larynx could be obtained, and the cuff was inflated. Gastric contents continued to pour out of the endotracheal tube, but the oropharynx could be quickly suctioned dry. A second endotracheal tube was rapidly inserted into an easily visualized larynx. The tube in the trachea was suctioned and O_2 was administered by positive pressure while checking the tube position. Gastric contents continued to drain from the esophageal tube for a full minute after the tracheal airway was secured. The esophageal tube was removed, a nasogastric tube was placed, and the remaining gastric contents were suctioned from the nasogastric tube.

The laparotomy was performed uneventfully under halothane-O_2 anesthesia with pancuronium for neuromuscular blockade. Blood gases drawn during the operating procedure showed a Pao_2 of 376 torr. Postoperatively, the patient was admitted to an intensive care unit with the endotracheal tube in place. Chest x-ray revealed a small right upper lobe infiltrate. On the 1st postoperative day, the infiltrate had begun to

*Assistant Professor, Department of Anesthesiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901.

Paper received: 3/22/76
Accepted for publication: 4/16/76

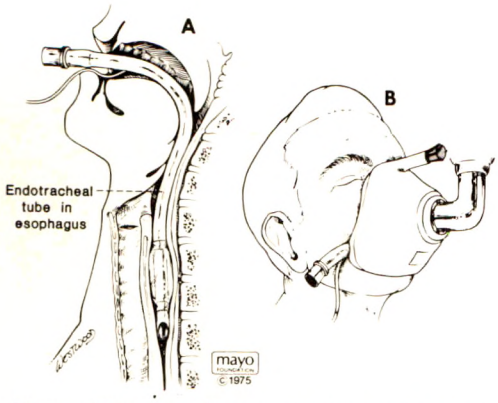


FIGURE. When gastric regurgitation occurs, an orotracheal tube (A) can be inserted blindly into the esophagus and the cuff inflated to provide an exit pathway for gastric contents. The mouth can be suctioned dry and mask ventilation (B) resumed, while the air entry pathway is thus separated from the exit pathway of gastric contents.

resolve, blood-gas tensions were acceptable, and the patient was extubated. The remainder of her recovery to discharge was uneventful.

DISCUSSION

It is often taught that, if vomiting occurs during the induction of general anesthesia, the first treatment should be tracheal intubation with a cuffed endotracheal tube. Many clinicians have witnessed a struggling colleague's attempt to intubate the trachea in a gush of regurgitant gastric contents with the suction at full power in the mouth. The real emphasis should be on protection of the airway from regurgitant material. From this viewpoint, the lungs can best be protected by separation of the exit pathway of regurgitant material from the entrance pathway of O_2.

The most common method of accomplishing this separation is by placing a cuffed tube into the trachea, but placement of a cuffed tube into the esophagus can also be effective. During regurgitation, intubation of the esophagus *or* trachea and inflation of the cuff can be lifesaving. A blindly placed tube may fortuitously enter the larynx. If, however, it enters the esophagus, effective separation of air entry and regurgitant outflow pathways can still be obtained, if the cuff is inflated and the tube left in place. The pharynx can be suctioned clear and positive-pressure ventilation can be immediately begun, if necessary, by excluding the esophageal tube from the mask area (figure). Another tube can be placed into the trachea as soon as feasible.

Thus, when the anesthesiologist encounters a patient regurgitating on induction, intubation of the trachea should be attempted immediately. If this is not possible, the esophagus should be intubated, and the cuff inflated. Then it is possible to quickly pursue whatever technical course is necessary to establish a stable separation of esophageal reflux and air entry, so that ventilation and oxygenation can be resumed.

Two possible complications of esophageal intubation with a cuffed tube should be considered: (1) the tube may perforate the esophagus and pass into the mediastinum, and (2) overinflation of the cuff may compress the trachea. Neither of these events is likely, however, and the small potential risk seems acceptable when weighed against the risk of uncontrolled regurgitation.

REFERENCES

1. Zuck D: A cuffed esophageal tube. Lancet 2:1017, 1955

2. Snow RG, Nunn JF: Induction of anaesthesia in the footdown position with a full stomach. Br J Anaesth 31:493-497, 1959

3. Sellick BA: Cricoid pressure to control regurgitation of stomach contents during induction of anaesthesia. Lancet 2:404-405, 1961

4. Stept WJ, Safar P: Rapid induction/intubation for prevention of gastric-content aspiration. Anesth Analg 49:633-636, 1970

5. Wycoff CC: Aspiration during induction of anesthesia—its prevention. Anesth Analg 38:5-13, 1959

The Anesthetic Potency of Lidocaine in the Rat

COSMO A. DiFAZIO, PhD, MD*
JAMES R. NIEDERLEHNER, MD†
ROBERT G. BURNEY, MD‡
Charlottesville, Virginia§

The anesthetic effect of lidocaine was evaluated in rats by determining the change in anesthetic requirement of cyclopropane MAC that was produced by blood concentrations of lidocaine in the clinically useful range. A linear reduction in anesthetic requirement was produced with concentrations up to 1 μg/ml. Further increases in lidocaine up to 5.5 μg/ml resulted in no further decrease in cyclopropane requirement. Lidocaine was found to contribute a maximum MAC fraction of 0.4.

RECENT concern with the problems associated with the administration of volatile anesthetics[1] and of atmospheric contamination[2] has placed greater emphasis on the development of alternative anesthetic technics. Intravenously administered lidocaine has been used with varying enthusiasm since the drug was introduced, either for analgesia or as part of a general anesthetic procedure.[3-5] However, no adequate measurements of the effective contribution of lidocaine to a general anesthetic procedure have been reported. The purpose of this study was to determine the anesthetic potency of lidocaine in rats by observing the reduction in the mean anesthetic concentration (MAC) of cyclopropane achieved by the addition of clinically useful levels of lidocaine.

METHOD

MAC was determined by the tail-clamp technic[6,7] in 25 cyclopropane-anesthetized rats weighing 239 ± 18 gm each. The external jugular vein was surgically exposed and cannulated and a slow (0.01 ml/min) constant infusion of lactated Ringer's solution was started. MAC was again determined after completion of the surgical procedure, and the control MAC was established as being the average of the values obtained before and after operation. The animal's rectal temperature was determined by a Yellow Springs temperature probe and maintained by a warming mattress.

A lidocaine bolus of 250 or 750 μg was followed by a constant infusion of 50, 75, 150, or 250 μg/min for up to 1 hour. MAC was again determined, beginning after the animal had received the lidocaine constant infusion for at least 15 minutes. Heart blood was assayed for blood lidocaine concentration by gas chromatography[8] immediately after MAC determination.

RESULTS

Control cyclopropane MAC (13.8%) was found (table 1) to be comparable to the previously reported MAC for cyclopropane,[9] and a linear reduction in MAC was observed with lidocaine concentrations up to

*Professor of Anesthesiology.
†Resident in Anesthesiology.
‡Assistant Professor of Anesthesiology.
§Department of Anesthesiology, University of Virginia Medical Center, Charlottesville, Virginia 22901.

Read at the 50th Congress of the International Anesthesia Research Society, March 14-18, 1976, Phoenix, Arizona.
Paper received: 3/22/76
Accepted for publication: 4/14/76

TABLE 1
Observed MAC Values During Lidocaine Infusion and During 2 Control Periods

Animal weight, gm	First control cyclo MAC	Second control cyclo MAC	Lidocaine MAC	Percent cyclo MAC reduction	Plasma lidocaine, μg/ml
252	14	14	12	14.3	0.34
240	14	12	9	30.8	0.62
230	14	13	10	25.9	0.37
243	14	14	10	28.6	0.51
225	16	15	10	35.5	0.89
210	14	14	10	28.6	0.67
213	14	14	10	28.6	0.65
249	13	13	12	7.7	0.14
—	15	15	13	13.3	0.38
265	14	14	11	21.4	0.53
283	15	14	9	37.9	1.00
240	13	12	9	28.0	0.57
240	13	13	10	23.1	0.41
220	14	14	9	35.7	5.52
243	14	14	9	35.7	2.49
236	14	14	7	50.0	1.85
220	13	13	8	38.5	1.32
252	14	13	7	48.1	1.01
223	15	14	9	37.9	3.46
232	14	14	7	50.0	3.05
235	15	14	7	51.7	4.47
260	12	12	7	41.7	3.21
245	14	14	9	35.7	3.69
220	14	14	13	7.1	0.39
260	13	13	12	7.7	0.23
Mean 239	13.96	13.60	9.54	30.45	1.51
SD 17.7	0.84	0.81	1.89	13.35	1.54

1 μg/ml (fig 1). Linear regression of the values below 1.1 μg/ml (1st part of curve in fig 1) produced the equation Y = 40.2X + 1.5 (lidocaine MAC equivalents = 40.2 lidocaine concentration + 1.5). The correlation coefficient was 0.93. A ceiling effect was noted at blood levels above 1 μg/ml. Further increases in lidocaine up to 5.5 μg/ml resulted in no further change in cyclopropane requirements. A mean reduction of 42 percent in cyclopropane MAC was observed with lidocaine concentrations of 1.1 to 5.5 μg/ml.

Gas chromatography allowed measurement of the lidocaine metabolites MEXG (monoethylglycinexylidide) and GX (glycinexylidide), concentrations of which were seen consistently to be less than 0.1 μg/ml and were noncontributory to the anesthetic effect.

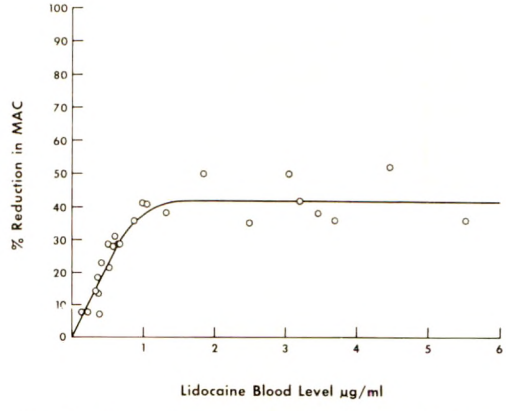


FIG 1. The percent reduction in anesthetic requirement (cyclopropane MAC) that results from increased lidocaine blood levels is shown. A ceiling effect is present above 1 μg/ml in blood lidocaine concentrations.

DISCUSSION

Concomitant use of IV lidocaine with other agents to produce general anesthesia has been reported by several authors. deClive Lowe[3] reported administering 750 mg of lidocaine in the first hour of varying procedures along with sodium thiopental

and N_2O. Steinhaus and Howland[4] and Phillips and coworkers[5] also reported on the administration of lidocaine, thiopental, and N_2O for general anesthesia, observing that lidocaine had an anesthetic effect which resulted in a 13 percent mean reduction in thiopental requirement. Blood levels of lidocaine were not determined.

In a variety of circumstances, lidocaine blood levels equal to or greater than those used in our experiment have been observed in man. Levels of 2 to 5 μg/ml have been sought for arrhythmia control.[10] Mean peak blood levels as high as 6.4 μg/ml have been reported with regional anesthesia.[11] These levels are considered safe for man. Convulsant levels are reported to be 8 to 10 μg/ml in unpremedicated man and 15 μg/ml in the rat.[12]

The rat has been previously established as a model for anesthetic requirements, and correlations between MAC and the oil/gas partition coefficient comparable to those found in man[16] and the dog have been observed (fig 2). A marked difference, however, exists between rat and man in the metabolic pathway of lidocaine. In the rat, large amounts of 3-hydroxy lidocaine and 3-hydroxy MEGX are produced (table 2). The anesthetic contribution of these metabolites which predominate in the rat are unknown. While the absolute anesthetic requirement and the percent reduction produced by lidocaine should show species variation, this experiment provides an approximation of what may be expected in man.

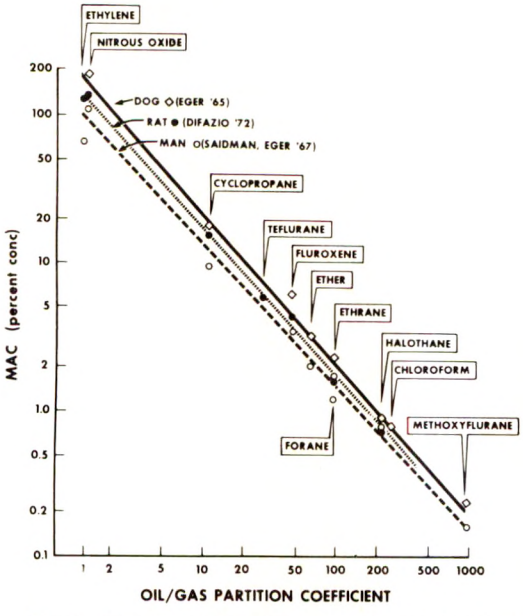


FIG 2. The correlation of anesthetic requirement (MAC) and the oil-gas partition coefficient is shown for man, rat and dog. Anesthetic requirements are highest for the dog, least for man and the rat is intermediate.

TABLE 2
Species Variation in Urinary Excretion of Lidocaine and Metabolites[17]

Compound	Percent of dose in urine	
	Rat	Man
Lidocaine	0.2	2.8
MEGX	0.7	3.7
GX	2.1	2.3
3-hydroxy-lidocaine	31.2	1.1
3-hydroxy-monoethylglycine-xylidide	36.9	0.3
2,6-xylidine	1.5	1.0
4-hydroxy, 2,6-xylidine	12.4	72.6

The combination of volatile and almost all other anesthetics has been shown to produce a purely additive effect,[9,13,14] such an effect resulting when the sum of the MAC fractions of the 1st and 2nd agents is equal to 1 MAC, although the result of combination of a MAC fraction of a fixed drug with a MAC fraction of a volatile anesthetic has not been established.

An additive effect appears present over a considerable dosage range (linear reduction in MAC) when morphine and meperidine are used as fixed drugs.[15] The MAC for these fixed agents, however, could not be established without encountering respiratory toxicity. In the present study, a MAC for lidocaine could not be established because a ceiling effect resulted. A mean maximum MAC fraction of lidocaine was established to be 0.4 MAC (maximum lidocaine MAC = 0.4).

The production of 0.4 MAC by low levels of lidocaine suggests that the addition of any anesthetic capable of contributing 0.6 MAC should result in the production of general anesthesia. In previous reports in man, however, both lidocaine and thiopental were required to supplement 70 percent N_2O (0.65 MAC). It would appear, therefore, that the anesthetic effect of lidocaine in man is considerably less than in the rat. Further studies in man are underway.

REFERENCES

1. Cascorbi HF, Gravenstein JS: Silent death. Anesthesiology 40:319-320, 1974

2. American Society of Anesthesiologists, Report of an Ad Hoc Committee on the Effect of Trace Anesthetics on the Health of Operating Room Personnel: Occupational disease among operating room personnel: a national study. Anesthesiology 41:321-340, 1974

3. de Clive-Lowe SG, Desmond J, North J: Intravenous lignocaine anaesthesia. Anaesthesia 13: 138-146, 1958

4. Steinhaus JE, Howland DE: Intravenously administered lidocaine as a supplement to nitrous oxide-thiobarbiturate anesthesia. Anesth Analg 37: 40-46, 1958

5. Phillips OC, Lyons WB, Harris LC, et al: Intravenous lidocaine as an adjunct to general anesthesia: a clinical evaluation. Anesth Analg 39:317-322, 1960

6. Eger EI II, Saidman LJ, Brandstater B: Minimum alveolar anesthetic concentration: a standard of anesthetic potency. Anesthesiology 26:756-763, 1965

7. Munson ES, Hoffman JC, DiFazio CA: The effects of acute hypothyroidism and hyperthyroidism on cyclopropane requirement (MAC) in rats. Anesthesiology 29:1094-1098, 1968

8. DiFazio CA, Brown RE: The analysis of lidocaine and its postulated metabolites. Anesthesiology 34:86-88, 1971

9. DiFazio CA, Brown RE, Ball CG, et al: Additive effects of anesthetics and theories of anesthesia. Anesthesiology 36:57-63, 1972

10. Gianelly R: Effect of lidocaine on ventricular arrhythmias in patients with coronary heart disease. N Engl J Med 277:1215-1219, 1967

11. Baid DP, Scott DB: The systemic absorption of local analgesic drugs. Br J Anaesth 37:394-404, 1965

12. Blumer J, Strong JM, Atkinson AJ Jr: The convulsant potency of lidocaine and its N-dealkylated metabolites. J Pharamacol Exp Ther 186:31-36, 1973

13. Cullen SC, Eger EI II, Cullen BF, et al: Observations on the anesthetic effect of the combination of xenon and halothane. Anesthesiology 31:305-309, 1969

14. Miller RD, Wahrenbrock EA, Schroeder CF, et al: Ethylene-halothane anesthesia. Anesthesiology 31:301-304, 1969

15. Hoffman JC, DiFazio CA: Anesthesia—sparing effect of pentazocine, meperidine and morphine. Arch Int Pharmacodyn 186:261-268, 1970

16. Saidman LJ, Eger EI II, Munson ES, et al: Minimum alveolar concentration of methoxyflurane, halothane, ether and cyclopropane in man: correlations with theories of anesthesia. Anesthesiology 28:994-1002, 1967

17. Boyes RN, Kennaghan JB: The tissue distribution, metabolism and excretion of lidocaine in rats, guinea pigs, dogs and man. J Pharmacol Exp Ther 180:454-463, 1972

LIDOCAINE METABOLISM. Congestive heart failure, as may follow acute myocardial infarction (AMI), may be associated with a decreased volume of drug distribution and slowed hepatic and renal elimination. As a result drug concentrations may be higher in patients with cardiac failure and the risk of drug toxicity increased. Plasma lidocaine concentrations during and after constant rate infusion (1.4 mg/min) were measured in 12 patients with AMI and 6 normal patients. Lidocaine concentrations were significantly higher in patients with cardiac failure than in normals. The mean values at the conclusion of infusion were 4.1 and 2.8 μg/ml respectively. The rate of decrease after drug infusion was always slower in patients with heart disease. The terminal plasma half-life was prolonged almost threefold (1.5 hours in normals). Impaired lidocaine metabolism probably reflects reduced hepatic blood flow associated with a low cardiac output. *(Prescott LF, Adjepon-Yamoah KK, Talbot RG: Impaired lignocaine metabolism in patients with myocardial infarction and cardiac failure. Brit Med J 1:939-941, 1976)*

Early Reversal of Postoperative Hypoxemia

A. EUGENE PFLUG, MD*
MICHAEL J. LINDOP, MD†
TERENCE M. MURPHY, MD‡
GEORDIS M. AASHEIM, MD§
HAROLD A. BECK, BS‖
Seattle, Washington**

Peridural analgesia was combined with the respiratory-stimulant effect of doxapram for intermittent hyperinflation of the lungs to reverse early postoperative (PO) hypoxemia following inhalation anesthesia for upper abdominal operations. Twenty unpremedicated men undergoing upper abdominal operations were studied for 5 hours in the recovery room. Ten of these patients received doxapram plus peridural analgesia; the other 10, doxapram plus morphine analgesia. Rectal temperature, Pa_{O_2}, Pa_{CO_2}, respiratory rate, exhaled minute ventilation ($\dot{V}_E$), tidal volume (V_T), and blood pressure and pulse were measured. The mean increase from control for $\dot{V}_E$ was 9.6 L/min and for V_T, 356 ml/breath during doxapram therapy for the morphine group. Corresponding values for the peridural group were 14.4 L/min for $\dot{V}_E$ and 660 ml/breath for V_T. Mean Pa_{O_2} for the morphine group decreased significantly from the corresponding preoperative value ($p<0.005$). Lack of significant change between preoperative and PO values for Pa_{O_2} for the peridural group would indicate that under the conditions of this study, early PO hypoxemia can be reversed by the combination of peridural analgesia with doxapram therapy.

HYPOXEMIA often follows inhalation anesthesia for upper abdominal or thoracic operations. It may be reversed by combining peridural analgesia with doxapram-induced hyperinflation of the lungs. In the present study, hypoxemia refers to a decrease greater than 15 percent in Pa_{O_2} within the first 5 postoperative (PO) hours, when both preoperative (control) and PO blood samples were obtained while the patient was breathing room air ($F_{IO_2} = 0.21$). Hypoxemia may persist for up to 5 days.[1-4] Voluntary stir-up regimes, IPPB with O_2, and CO_2 rebreathing have failed to reverse or shorten such hypoxemia.[2,5]

The condition can be circumvented in the recovery room by the use of supplemental inhaled O_2 via disposable face mask or nasal prongs.[4] The Pa_{O_2} value under these conditions will usually equal or exceed preoperative Pa_{O_2} values on room air, if the PO arterial blood is obtained while the patient is breathing supplemental O_2.[4] However, supplemental inhaled O_2 does not, by itself, correct the causes of early PO hypoxemia. When the O_2 is removed, the Pa_{O_2} on room air usually falls to pretreatment levels.[6]

The level of the hypoxemia may be most

*Assistant Professor.
†Instructor.
‡Assistant Professor.
§Assistant Professor.
‖Medical Student.
**Department of Anesthesiology, Anesthesia Research Center, University of Washington School of Medicine, Seattle, Washington 98185.

This study was supported in part by USPHS Grant GM 15991-05 from the National Institute of General Medical Sciences, Grant RR-133 from the General Clinical Research Center Program of the Division of Research Resources, National Institutes of Health, and a Grant from Sterling-Winthrop Research Institute, Division of Sterling Drug Incorporated, Rensselaer, New York.

Paper received: 10/6/75

Accepted for publication: 1/30/76

critical during the first 5 to 6 hours after anesthesia.[4] If recovery-room patients are transferred to their ward beds within 1 to 2 hours after anesthesia without supplemental O_2, they may become hypoxemic.

Pain on sighing or deep breathing may reduce pulmonary compliance and functional residual capacity associated with the hypoxemia.[7,8] Narcotic analgesia plus the respiratory stimulant effect of doxapram has been used for reversal;[9] however, this combination is not always successful, and pain due to incomplete narcotic analgesia may restrict the respiratory response to doxapram. Segmental peridural analgesia provides excellent pain relief but does not, by itself, correct the hypoxemia.[3,5]

METHODS

Twenty unpremedicated men undergoing upper abdominal operations were studied for 5 hours in the recovery room. They were divided into 2 groups, each consisting of 10 patients who randomly received either (1) peridural or (2) morphine analgesia with doxapram hyperinflation. Informed consent was obtained from all subjects. Patients were accepted for study if they were not hypoxemic, had normal chest x-rays, no uncontrolled systemic disease, and no history of vascular hypertension, seizures, or cerebrovascular accidents.

Preoperatively, a Teflon catheter was inserted into a radial artery for blood sampling. All patients received general anesthesia with halothane (0.5 to 1.5%) and N_2O-O_2 (60:40). Pancuronium was used for muscle relaxation. Ventilation was maintained with a bird® Mark IV anesthesia ventilator. Following endotracheal intubation, patients in the peridural group had a catheter inserted at T10-11 but without injection of local anesthetic solution. Patients in the morphine group were not so catheterized.

Postoperative peridural analgesia was obtained in the operating room by injecting 6 to 8 ml of 0.5 percent bupivacaine, which produced segmental analgesia localized to the area of surgical incision. Analgesia was maintained by intermittent peridural reinjection and was not supplemented by other forms of pain relief. Dermatome levels of analgesia were evaluated by pinprick.

In the morphine group, morphine was administered in IM doses of 10 to 15 mg, depending on patient size and age, at intervals calculated to keep the patient comfortable but not obtunded (3 to 5 hr).

No attempt was made to evaluate directly the magnitude of pain experienced by any individual patient or any group of patients. The following variables were measured both preoperatively and postoperatively: rectal temperature, Pa_{O_2}, Pa_{CO_2}, respiratory rate, exhaled minute ventilation ($\dot{V}_E$), tidal volume (V_T), blood pressure (BP), and pulse.

Doxapram intermittent hyperinflation was started in the recovery room 1 hour postoperatively and followed baseline resting values. The IV doxapram injection was then repeated hourly for 4 hours. Doxapram dosage was individualized (0.5 to 2 mg/kg) to obtain a V_T increase of 2 to 3 times resting values. All patients received 0.5 mg/kg for the first or test dose. All doxapram infusions were diluted with 1 N saline solution to a final volume of 8 ml, which was injected into the IV tubing over a 60-second period. Further IV dosage was determined by the response to the test dose.

Supplemental O_2 was provided for 5 minutes before, during, and 10 minutes after doxapram hyperinflation, to prevent O_2 debt due to increased physical activity. The O_2 was supplied via anesthesia mask, Hans Rudolph nonrebreathing valve, and a Puritan humidifier, set to deliver 40 percent O_2. $\dot{V}_E$ was monitored during doxapram hyperinflation by attaching a Wright respirometer to the exhalation port of the Hans Rudolph valve. Respiratory rate was counted by visual observation of chest movement, and V_T was calculated by dividing $\dot{V}_E$ by respiratory rate for 1 minute. Pulse and BP were obtained 5 minutes after the doxapram injection, as this is reportedly the time of peak cardiovascular changes due to doxapram.[9]

Arterial blood-gas and pH samples were obtained before anesthesia induction in the operating room and 30 minutes postoperatively in the recovery room, and again 50 minutes after doxapram and O_2 therapy, hourly for 5 hours. In all cases, samples were obtained with the patient continuously breathing room air (F_{IO_2} = 0.21) for at least 30 minutes.

Rectal temperature was obtained before drawing blood samples. Arterial blood-gas analysis was completed with an Instrumentation Laboratories 113 blood gas analyzer, with appropriate corrections for body temperature. Preoperative and 30-minute PO measurements were used as control values.

Single values for 1 to 4-hour PO data

TABLE 1
Patient Data and Significant Measurements at 30 Minutes to 5 Hours PO (Means ± SD)

	Age, yr	Weight, kg	Height, cm	Maximum doxapram injection, mg	Rectal temperature 30 min PO, C	Rectal temperature 5 hours PO, C	△ temperature 30 min to 5 hr PO, C
I. Morphine group	54.8	75.8	178	67.0	36.3	37.6	1.3*
(n =10)	±13.9	±9.7	±7	±14.9	±0.66	±0.32	±0.43
II. Peridural group	44.3	71.8	176	75.0	36	37.8	1.8*
(n =10)	±11.3	±15.4	±10	±15.8	±0.55	±0.6	±0.82

*Significant change, $p<0.001$, for designated time periods within a single group.

were obtained by finding the mean for results for PO hours 1, 2, 3, and 4. Also, single values for 2 to 5-hour data (Pao_2, $Paco_2$, rectal temperature) represent the mean for PO hours 2, 3, 4, and 5. Significance was determined by Student's *t*-test for paired data.

RESULTS

No significant difference was noted between mean values for the morphine and peridural groups for age, weight, height, doxapram dosage, or body temperature (table 1). However, a significant ($p<0.001$) change in mean values for rectal temperature was noted within both groups. All patients revealed a relative hypothermia in 30-minute PO rectal temperature compared with their 2 to 5-hour values.

No significant difference was found in BP and pulse mean values between the 2 groups (table 2). However, a significant change ($p<0.005$) was noted within the morphine group for both these values after doxapram injection.

No significant difference in respiratory rate, $\dot{V}_E$, or V_T between groups was found (table 3). However, doxapram did produce a significant rise in respiratory rate in the morphine group ($p<0.01$) and a similar increase in $\dot{V}_E$ and V_T for both groups ($p<0.001$). The mean increase from control for the morphine group was 9.6 ± 4.9 L/min for $\dot{V}_E$ and 356 ± 213 ml/breath for V_T. For the peridural group, the mean increase was 14.4 ± 4.7 L/min for $\dot{V}_E$ and 660 ± 276 ml/breath for V_T.

A significant decrease in mean Pao_2 was noted between preoperative and postoperative values in the morphine group (77.3 versus 66 torr; $p<0.005$) (table 4). This drop in Pao_2 is characteristic of the hypoxemia under study. A significant difference was also noted (1.1 versus −7.1 torr; $p<0.01$) between the peridural and morphine groups. The lack of change between mean preoperative and postoperative values for Pao_2 for the peridural group (77 versus 78 torr) would indicate that, under the conditions of this study, the hypoxemia was reversed by the combination of peridural analgesia with doxapram. Figure graphically represents these changes.

The doxapram as used in this study produced a respiratory response within 40 to

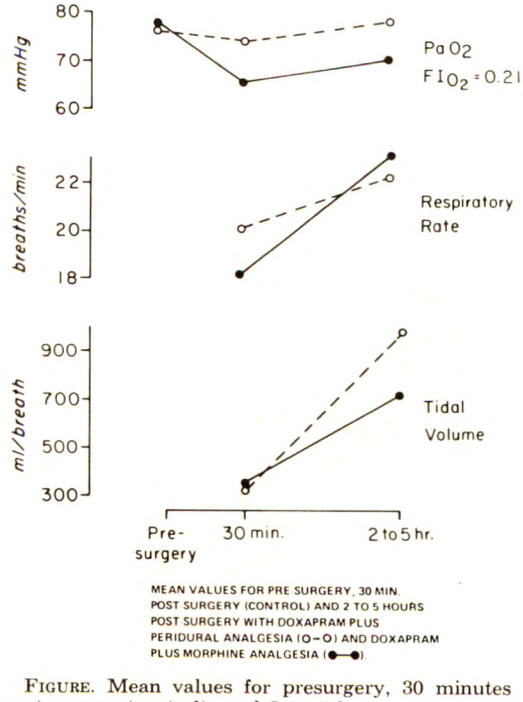


FIGURE. Mean values for presurgery, 30 minutes postsurgery (control), and 2 to 5 hours postsurgery with doxapram plus peridural analgesia (0-0) and doxapram plus morphine analgesia (0--0).

TABLE 2
Cardiovascular Data Compared (Means ± SD)

	Blood pressure, torr				Pulse, beats/min				
	Preop	30 min postop	1-4 hr postop	Δ preop to 30 min postop	Δ preop to 1-4 hr postop	Preop	30 min postop	1-4 hr postop	Δ preop to 30 min postop	Δ preop to 1-4 hr postop
I. Morphine group	117/77	125/81	139/89	11/5	24/13*	76	77	95	2	21*
(n = 10)	±14/10	±25/14	±20/10	±19/14	±20/10	±12	±15	±21	±8	±16
II. Peridural group	114/72	105/67	116/73	−9/−5	3/1	77	77	86	0	10
(n = 10)	±22/10	±15/13	±16/10	±25/16	±24/14	±10	±12	±7	±15	±14

*Significant changes, $p<0.005$, for designated time periods within a single group.

60 seconds from beginning of injection, developed a maximum response at ± 1 minute after injection, and the effect disappeared 2 to 3 minutes after the onset of respiratory stimulation. A mean doxapram dose of ± 1 mg/kg body weight (table 1) was required to obtain an increase in V_T of 2 or 3 times the resting value (table 3). In the morphine group, 4/10 patients and in the peridural group 1/10 patients did not achieve the desired V_T increase. The dosage of doxapram was often decreased in the morphine group patients to reduce the pain associated with increased respiratory effort. No major adverse reaction due to doxapram was noted in either group.

DISCUSSION

Aldrete[4] reported the incidence of PO hypoxemia to be about 75 percent. The risk of serious hypoxemia is increased by advanced age, obesity, multiple system disease, trauma, advanced chronic lung disease, upper abdominal or thoracic operations, and/or prolonged shivering in the recovery room.[4] Tissue hypoxia resulting from hypoxemia can result in serious complications, such as metabolic acidosis, cardiac arrhythmias, vascular hypotension, and respiratory insufficiency.[4]

Schmidt and colleagues[10] found 9 cm of continuous positive airway pressure (CPAP) for 24 hours by nasal intubation and spontaneous ventilation useful in preventing hypoxemia in high-risk patients. Arterial blood-gas tensions were improved, and none of the CPAP patients developed PO respiratory insufficiency. This method, however, involves the risk of complications inherent in nasal intubation, CPAP, and increased levels of narcotic analgesia.

The Pain Factor.—Breathing with a V_T of 700 to 1000 ml/breath at a rate of 20 to 25/min within 1 or 2 hours after upper abdominal incision may induce considerable reflex pain. Conventional morphine analgesia does not completely abolish the pain associated with such rapid deep breathing. Segmental peridural analgesia abolishes the somatic and some, but not all, of the visceral pain.

Some of the patients in our peridural analgesia group complained of vague deep abdominal discomfort and/or shoulder pain when deep breathing. This discomfort may have represented an incomplete block of deep visceral or phrenic nerve reflexes. The

TABLE 3

Respiratory Data Compared

	Respiratory rate, breaths/min			Minute ventilation, L/min			Tidal volume, ml		
	30 min postop	1-4 hr postop	△	30 min postop	1-4 hr postop	△	30 min postop	1-4 hr postop	△
I. Morphine group (n = 10)	13	21	+8	7.0	16.6	9.6	540	783	243
	24	29	+5	11.6	12.3	0.7	483	416	−67
	17	18	+1	4.7	13.2	8.5	277	775	498
	13	25	+12	3.3	22.3	19.0	255	886	631
	31	32	+1	13.2	19.2	6.0	426	605	179
	16	26	10	3.4	14.4	11.0	212	531	319
	16	19	3	3.5	12.3	8.8	219	684	465
	24	23	−1	4.2	17.7	13.5	175	793	618
	15	23	+8	5.0	16.6	11.6	333	720	387
	14	17	+3	8.5	15.3	6.8	600	885	285
Mean	18.3	23.3	5.0*	6.4	16.0	9.6†	352	708	356†
± SD	±6.0	±4.8	±4.3	±3.6	±3.2	±4.9	±150	±152	±213
± SE	±1.9	±1.5	±1.4	±1.1	±1.0	±1.5	±48	±48	±67
II. Peridural group (n = 10)	19	21	2	6.4	29.0	22.6	337	1359	1022
	28	25	−3	6.0	21.0	15.0	214	854	640
	13	18	+5	6.1	18.0	11.9	470	1018	548
	18	25	+7	6.0	11.8	5.8	333	501	168
	20	23	+3	9.0	23.0	14.0	450	1142	692
	18	18	0	5.1	23.3	18.2	283	1273	990
	22	23	+1	7.3	23.5	16.2	332	1014	682
	23	19	−4	4.8	21.6	16.8	209	1176	967
	25	23	−2	9.6	18.8	9.2	394	831	447
	15	26	+11	4.2	18.6	14.4	280	722	442
Mean	20.1	22.1	2	6.5	20.9	14.4†	329	989	660†
± SD	±4.5	±3.0	±4.7	±1.7	±4.5	±4.7	±88	±265	±276
± SE	±1.4	±0.9	±1.5	±0.6	±1.4	±1.5	±28	±84	±87

*Significant change, $p<0.01$, for designated time periods within a single group.

†Significant change, $p<0.001$, for designated time periods within a single group.

degree to which pain restricted deep breathing in our study is best estimated by the $\dot{V}_E$ response to doxapram under standardized conditions ($\dot{V}_E$ = 16 L/min for the morphine group versus 20.9 L/min for the peridural group) of factors other than analgesia which might influence hypoxemia (sex, age, weight, height, preoperative Pao_2, intraoperative anesthesia, abdominal incision, hypothermia, and IV doxapram dosage).

The hypoxemia noted in our morphine group (16% drop in Pao_2 between preoperative and 30 minutes postoperatively) is close to the changes in Pao_2 under similar conditions reported by Winnie,[9] Aldrete,[4] and Spence.[3] This early decrease in arterial blood oxygenation was also found with peridural analgesia without doxapram for patients with upper abdominal incisions.[3,5]

We noted that a 1 mg/kg injection of doxapram administered to the morphine group patient resulted in a V_T less than that achieved with the same dose in a patient given a peridural block (table 3). The morphine group patients also complained of pain more often than the peridural-block patients. We assumed that the reduced V_T resulted from increased abdominal pain. However, Mitchell and Herbert[11] showed in cats that respiratory stimulation by doxapram in the recommended therapeutic dosage range (0.5 to 2 mg/kg) is through stimulation of the carotid chemoreceptors. Ventilation response to respiratory stimulation can be reduced by a morphine-associated shift in the CO_2 response curve.[12] Therefore, the carotid chemoreceptor response to doxapram stimulation may also be reduced by morphine. Morphine analgesia alone, or combined with pain, may account for the reduction in V_T noted with doxapram in our morphine group.

TABLE 4
Pao_2 Values Compared, torr

	Preop	30 min postop	2-5 hr postop	△ preop to 30 min postop	△ preop to 2-5 hr postop
I. Morphine group (n = 10)	74	71	70	−3	−4
	83	66	74	−17	−9
	89	63	75	−26	−14
	78	75	86	−3	+8
	80	64	73	−16	−7
	70	58	56	−12	−14
	70	66	53	−12	−17
	71	64	67	−7	−4
	78	69	75	−9	−3
	80	64	73	−16	−7
Mean	77.3	66	70.2	−12.1*	−7.1
± SD	±6.2	±5	±9.6	±7.5	±7.2
± SE	±2.0	±1.7	±3.0	±2.5	±2.3
II. Peridural group (n = 10)	64	74	65	−4	+1
	69	54	72	−15	+3
	79	80	86	+1	+7
	87	83	85	−4	−2
	86	87	81	+1	−5
	75	79	78	+4	+3
	75	65	71	−10	−4
	87	74	82	−13	−5
	79	77	91	−2	+12
	68	68	69	0	+1
Mean	76.9	74.1	78	−4.2	1.1†
± SD	±8.2	±10.2	±8.4	±6.8	±5.5
± SE	±2.6	±3.4	±2.7	±2.3	±1.7

*Significant change, $p<0.005$, for designated time periods within a single group.

†Significant difference, $p<0.01$, between values for groups.

Peridural analgesia in our study usually extended from T-6 down to T-12. This block with 0.5 percent bupivacaine produced satisfactory analgesia with minimal intercostal muscle paralysis. Rib movement during doxapram hyperinflation appeared normal clinically and $\dot{V}_E$ under these conditions compares closely with reported responses to doxapram in adult males without an operation or analgesia (peridural $\dot{V}_E = 20.9$ L/min, no anesthesia $\dot{V}_E$ = 14.7 L/min.)[13]

Winnie and associates[9] studied the effect of doxapram lung hyperinflation on hypoxemia in patients who had upper abdominal incisions and morphine analgesia. They gave doxapram as an IV bolus of 1 mg/kg at PO times 0, 1, and 4 hours and then every 4 hours for a total of 8 injections (24 hours). The respiratory response to doxapram they reported (change in respiratory rate = 5.5/min, $\triangle V_T$ = 314 ml, $\triangle \dot{V}_E$ = 14.3 L) is close to our morphine group values (table 3). Patients given doxapram demonstrated a return of Pao_2 values to preoperative levels 20 hours postoperatively. It must be noted, however, that their doxapram infusions were at 4-hour intervals rather than our 1-hour intervals.

Aldrete[4] studied over a one-hour period the effect of 1 mg/kg bolus of doxapram IV on patients with PO hypoxemia given morphine, reporting no improvement in PO arterial oxygenation for their doxapram group.

In our study, the sympathetic nervous system blockade accompanying peridural analgesia may account for the reduced cardiovascular response to doxapram noted in the peridural-block patients (table 2). The definite increase in blood pressure and pulse associated with doxapram therapy in the morphine group (△ BP = 24/13, △ pulse = 21) was almost completely abolished by the sympathetic blockade in the peridural group (△ BP = 3/1, △ pulse = 10).

REFERENCES

1. Diament ML, Palmer KNV: Postoperative changes in gas tensions of arterial blood and in ventilatory function. Lancet 2:180-182, 1966

2. Knudsen J: Arterial oxygen tension in the postoperative course after upper abdominal and thoraco-abdominal operations. Acta Anaesthesiol Scand Suppl 37:161, 1970

3. Spence AA, Smith G: Postoperative analgesia and lung function: a comparison of morphine with extradural block. Br J Anaesth 43:144-148, 1971

4. Aldrete JA: Management of the postanesthetic patient. Clin Trends Anesth 3:1-4, 1973

5. Pflug AE, Murphy TM, Butler SH, et al: The effects of postoperative peridural analgesia on pulmonary therapy and pulmonary complications. Anesthesiology 41:8-17, 1974

6. Conway CM, Payne JP: Postoperative hypoxaemia and oxygen therapy. Br Med J 1:844-845, 1963

7. Schwartz SI, Dale WA, Rahn H: Deadspace rebreathing tube for prevention of atelectasis. JAMA 163:1248-1251, 1957

8. Egbert LD, Bendixen HH: Effect of morphine on breathing pattern. JAMA 188:485-488, 1964

9. Winnie AP, Gladish JT, Angel JJ, et al: Chemical respirogenesis. II: Reversal of postoperative hypoxemia with the "pharmacologic sigh." Anesth Analg 50:1043-1055, 1971

10. Schmidt GB, Bennett EJ, Kotb KM, et al: Prophylactic continuous positive airway pressure may curb adult respiratory distress syndrome. Clin Trends Anesth 4:1-4, 1974

11. Mitchell RA, Herbert DA: Comparison of potency of doxapram and hypoxia on stimulating carotid body chemoreceptors and ventilation in anesthetized cats. American Society of Anesthesiologists, Abstracts of Scientific Papers, 1973, pp 235-236

12. Hornbein TF, Sorensen SC: The chemical regulation of ventilation, Physiology and Biophysics. Edited by TC Ruch, HD Patton. Philadelphia, WB Saunders Company, 1974, p 384

13. Miller MJ, Fiedler HT: Pharmacologic effects of doxapram in the awake human. J Am Geriatr Soc 13:160-165, 1965

INTERNATIONAL CALENDAR

1976

December 26-30	Maharashtra State, India: Indian Society of Anaesthesiologists 26th Annual Conference. For information: Dr. A. I. Chruva, President, c/o Dr. N. K. Misra, I.M.A. Building, Medical Association Road, Patna-80004, India.
December 5-11	Belem, Para, Brazil: Society Brasileira de Anestesiologia 23rd Brazilian Congress of Anaesthesiology. For information: Dr. Joao Brenha Ribeiro, Rio de Janeiro, ZC-02, Guanabara, Brazil, South America.

1977

May 11-13	Karl Marxstadt, East Germany: Society of Anesthesiologists & Reanimation of the GDR Biannual Congress, "Anaesthesia in Emergencies and Shock" and "The Anaesthesiologists and the Perinatal Period." For information: Prof. Wolfgang Rose, 301 Magdeburg, Leipziger Strasse 44, East Germany.
October 21-23	Kuala Lumpur, Malaysia: The Malaysian Society of Anaesthesiologists Second Malaysian Congress of Anaesthesiologists, General Hospital, Kuala Lumpur, Malay. For information: The Hon. Secretary, Second Malaysian Congress of Anaesthesiologists, P.O. Box S-20, Sentul, 124, Jalan Pahang, Kuala Lumpur, Malaysia.

Local Anesthetic Agents—Pharmacologic Basis for Use in Obstetrics: A Review

LARRY SALTS, MD*
MARYANN OTT, MS†
PHILIP D. WALSON, MD‡
Tucson, Arizona§

Because of minimal effects on mother and fetus, regional anesthetic technics are widely employed for labor and delivery. However, the literature describes at least 35 fetal and neonatal deaths and a frightening incidence of fetal distress associated with paracervical block for 1st-stage labor. Continuous lumbar epidural anesthesia for 1st-stage labor has also been associated with fetal distress, but this is minimal and no deaths have been reported. Bupivacaine, a relatively new, long-lasting local anesthetic, is extremely toxic when administered paracervically, but no deaths have been reported with its use for epidural anesthesia. While choice of method and agent must be individualized, continuous lumbar epidural block with bupivacaine appears as effective as and less often dangerous to the fetus than paracervical block.

PAIN during childbirth may be controlled by hypnosis, general anesthesia, systemic narcotic administration, and numerous local anesthetic procedures. Local anesthetics reversibly terminate nerve conduction; therefore, pain impulses originating in specific body regions may be abolished selectively while the patient retains consciousness. There is a popular belief that obstetric block with local anesthetics is safer for the fetus than use of potent general anesthetics. However, local anesthetics are rapidly absorbed into the maternal circulation and subsequently presented to the placenta.

Since Bromage and Robson[1] first reported placental transmission of a local anesthetic agent in 1961, many studies have established that these agents can cause severe fetal toxicity and that fetal or neonatal death can result.

This review focuses on the types of block and the local anesthetic agents most commonly used for the relief of 1st-stage labor pain. Before the drug-block combination with the best risk:benefit ratio can be selected, the pharmacokinetic aspects of the drugs that determine fetal toxicity must be understood, as must the relationships between technics, drugs, and their neuroanatomic rationale and potential risks. Basic also is an understanding of the separate neuroanatomic pain pathways of the different stages of labor.

I. LOCAL ANESTHETIC AGENTS

Characteristics.—In general, local anesthetics consist of 3 parts: (1) a lipophilic aromatic group, (2) a tertiary or secondary amine group, and (3) an ester or amide linkage. The class of local anesthetic agent

*Fellow, Clinical Pharmacology, Department of Anesthesiology.
†Graduate Student, Department of Toxicology.
‡Assistant Professor, Departments of Pharmacology and Pediatrics.
§University of Arizona Medical Center, Tucson, Arizona 85724.

This study was supported in part by NIH Institutional Research Fellowship Grant #GM00071-01.
Paper received: 11/7/75
Accepted for publication: 3/4/76

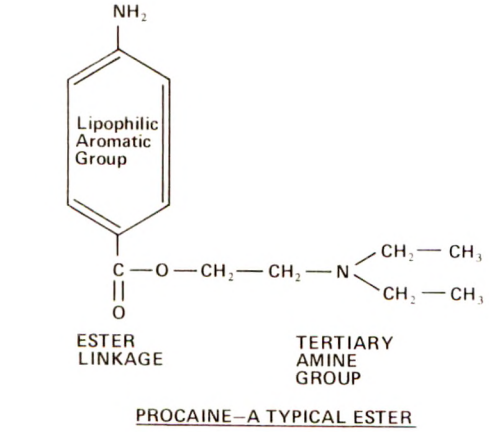
TABLE 1
General Characteristics of the Major Local Anesthetic Drugs

Local anesthetic	Concentration, percent	pKa	Duration of action, hr	Maximum dosage, mg	Adult toxic blood level, μg/ml	Placental transfer
Amide						
Lidocaine	1.0-1.5	7.9	1¼-3	500	5	Yes
Mepivacaine	1.0-1.5	7.6	1½-2½	500	6	Yes
Bupivacaine	0.24-0.50	8.1	3¼-7	200-500	4	Yes
Ester						
Procaine	1.0-2.0	8.9	¾-1½	1000	ND*	Yes
2-chloroprocaine	2.0	8.9	¾-1	1000	ND	Probably
Tetracaine	0.15-0.25	8.5	3½-6	200	ND	Probably

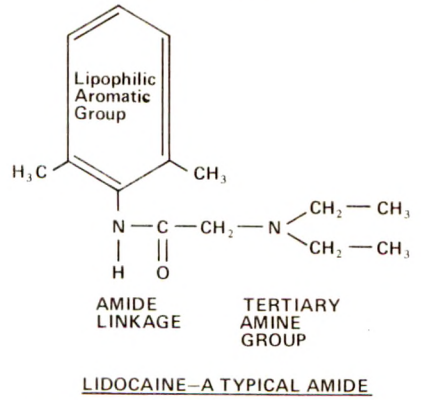
*ND = no data.

is determined by the linkage. Table 1 illustrates the general characteristics of the better known agents of the two classes.

Values for duration of action in table 1 apply to peripheral nerve blocks in general.



PROCAINE–A TYPICAL ESTER



LIDOCAINE–A TYPICAL AMIDE

FIG 1. Chemical characteristics of the two classes of local anesthetics.

Longer values are obtained when epinephrine is added to the anesthetic solution.[2] Studies of the duration of paracervical blocks show a different pattern. Freeman's group[3] found that paracervical blocks lasted about 1½ hours with all the agents employed in their study (procaine, tetracaine, cyclaine, nupercaine, and lidocaine) as long as the solution contained epinephrine. While cyclaine is an ester and nupercaine is an amide, both are very toxic. Paracervical block with 1 percent mepivacaine was found to give a mean duration of action of 1¼ hours in 1 series.[4] Other observers reported that 0.25 percent bupivacaine paracervical block lasted a mean of slightly less than 1½ hours, but 2⅔ hours with epinephrine.[5] Gudgeon[6] reported that paracervical block with 0.25 percent bupivacaine lasted a mean of 3 hours.

Despite these studies, one of the amides is usually chosen because this class is generally believed to provide a longer duration of action than the esters. Amides are preferred because labor usually lasts between 3 to 6 hours after the first paracervical block.[4] Paradoxically, however, paracervical block with epinephrine containing ester-linked local anesthetics can last as long as paracervical block with most of the amide-type agents.[3]

Metabolism.—An advantage of the esters is that systemic absorption does not result in high fetal levels because these agents are rapidly hydrolyzed by maternal plasma cholinesterases.[7] The amides must be metabolized in the liver; thus higher concentrations of amides are available to enter the fetal circulation. Therefore, amides may well be more toxic to the fetus and/or the mother than an equipotent dose of an ester.

Although these concepts about the metabolism of local anesthetics are true in general, details of the metabolism of the amide-linked local anesthetic agents in human fetuses and neonates have become available only recently. Studies by the Weiss group[8] and by Yaffe and coworkers[9] indicate that the human neonate is deficient in some drug-metabolizing enzymes, such as those required for hydroxylated metabolites of mepivacaine. Meffin and colleagues[10] reported that the ratios of N-demethylated, 3-hydroxy and 4-hydroxy metabolites to unchanged mepivacaine are lower in the neonate than in the adult. However, decreased neonatal metabolism may be protective in that the demethylated or de-ethylated amide metabolites appear to be more toxic than the parent compound.

Excretion. — Meffin showed that both adults and neonates excrete anilide local anesthetics almost entirely via the kidneys, but the adult excretes less than 5 percent of a dose as unchanged mepivacaine, and the neonatal kidney can clear the unchanged drug.[10]

Ostheimer's group[11] have shown that the neonate is able to N-de-ethylate bupivacaine to 2,6 pipecoloxylidide (PPX). Although the mothers excreted both bupivacaine and PPX in the urine, neonates rarely eliminated unchanged bupivacaine but all infants excreted PPX, beginning at about 12 hours and ending by 48 hours.

Placental Transfer. — Local anesthetics used for obstetric anesthesia are transferred across the human placenta to the fetus (Shnider and Way[12]). Placental transfer of these agents occurs by simple diffusion. The major drug factors contributing to this transfer are lipid solubility, ionization constant, size or molecular weight, protein binding, acid-base status of the patient, and electrochemical gradient.[7,13,14]

Maternal Toxicity.—Regardless of metabolic pathways, all local anesthetics are associated with some toxicity. Most of the available data on human toxicity have come from reports of the clinical use of these agents for delivery.

Foldes and associates,[15] studying the toxicity of lidocaine and 3 ester-linked local anesthetics in 12 adult male volunteers, described "generalized twitchings, convulsions, severe breathing difficulties, loss of consciousness, or total disorientation." The esters studied by this group were procaine, 2-chloroprocaine, and tetracaine. Generalized convulsions developed in 1 volunteer given tetracaine at 0.125 mg/kg/min IV. Three of 10 patients tolerated the procaine infusion (1 mg/kg/min) for 25 minutes. None of the 10 volunteers given a lidocaine infusion (0.5 mg/kg/min) tolerated this drug for more than 18 minutes. Because of pseudocholinesterase activity, plasma levels of procaine and 2-chloroprocaine were too low to be determined at the end of the experiments. Therefore, while the esters appeared less toxic than the amide, lidocaine, in these adult volunteers, the ester-linked agents obviously also have some toxic effects.

Lidocaine, mepivacaine, and bupivacaine were studied by Jorfeldt and colleagues[16] in dogs and man. Lidocaine and mepivacaine induced the same subjective symptoms as those observed by Foldes in volunteers. Bupivacaine produced no objective signs of toxicity other than slight eyelid numbness. Again, lidocaine convulsions were induced in 1 volunteer at a plasma concentration of 5 μg/ml. Jorfeldt's data suggest that generalized convulsions may be elicited when plasma concentrations reach 6 μg/ml of mepivacaine and 4 μg/ml of bupivacaine.

Despite the fact that these adult toxicity studies were conducted with intravenously infused local anesthetics, the data are pertinent because all drugs are systemically absorbed, regardless of the site of injection or the intended site of action. After absorption into the maternal blood stream, local anesthetics are subject to the pharmacokinetic factors which normally affect drug action and are subsequently presented to the placenta.

Fetal Toxicity.—Signs of fetal toxicity develop at plasma concentrations of the local anesthetics well below those plasma levels which are tolerated by adults. Fetal and neonatal toxicity is manifested by tachycardia, bradycardia, acidosis, apnea, convulsions, and death. Heyman[17] has correlated tachycardia with in-utero convulsions in experimental animals. Since the toxic reactions of the fetal myocardium and central nervous system appear to be a result of direct local anesthetic action,[17] O_2 and atropine will not reverse these effects.[18]

Shnider and Way[12] reported that within 3 to 5 minutes of detection of lidocaine in the maternal arterial circulation, the drug was transferred across the placenta to the fetus. Umbilical venous concentration of lidocaine was 53 percent of that simultaneously found in the maternal artery. At a low

physiologic concentration (2 μg/ml), practically all the lidocaine is plasma-protein bound. At higher concentrations, 30 percent is unbound. This concentration-dependent binding of lidocaine explains the large transplacental concentration gradient at high plasma concentrations of the drug.[19]

Morishima's group[20] reported the ratio of the mepivacaine concentration in the umbilical vein to the maternal antecubital vein concentration as 0.71/1 at 60 minutes after epidural anesthesia. Martin and coworkers[21] reported a ratio of 0.54 at 60 minutes after paracervical block.

The placental transfer of bupivacaine follows closely the pattern reported for lidocaine.[22] The ratio of umbilical to maternal plasma concentration at delivery varies from 0.14 to 0.86. There does not appear to be an obvious explanation for the wide patient-to-patient variation in placental transfer of either bupivacaine or lidocaine, but bupivacaine values for placental transfer are lower than those for mepivacaine or lidocaine.

Probably the most commonly observed toxic effects of local anesthetics on the fetus are bradycardia and acidosis. The cause of fetal bradycardia is subject to some controversy. Teramo and Widholm[23] suggested that the local anesthetics depress the fetal myocardium and CNS directly. On the other hand, Jung's group[24] contended that the changes are due to a disturbance in placental and umbilical blood flow. Most of the investigators seem to agree that the bradycardia represents the pharmacologic effect of the local anesthetic on the fetus, and it is possible that both mechanisms are responsible.

Infants with lidocaine levels greater than 3 μg/ml show a pattern of depression similar to that seen with mepivacaine.[12] Shnider also notes that the toxic threshold (depressed ventilation and abolished cutaneous reflexes) in the neonate is half that of the adult. The additive effects of birth asphyxia, drug depression, and a lower blood/brain barrier to the drug in the infant is a possible explanation. An inverse relationship between arterial P_{CO_2} and the threshold for lidocaine toxicity in experimental animals has also been demonstrated.[25]

II. REGIONAL BLOCK IN OBSTETRICS

Pain Pathways.—The pain of the 1st stage of labor originates from both the corpus and cervix of the uterus. The major sensory component is the sympathetic nervous system. The sympathetic fibers from the corpus uteri originate in the posterior cervical ganglia and the pelvic plexus and ganglia before eventually entering the spinal cord with the posterior roots of T-11 and T-12. Higher cord levels may be encountered in a few patients who receive alternate afferent pathways along the ovarian vessels.[26]

With the beginning of the 2nd stage of labor at full cervical dilation, the descent of the fetus causes the painful impulses to shift from the uterus to the distending vagina, perineum, and vulva. Since the mons pubis and the anterior portions of the labia majora are stimulated minimally during routine deliveries, 2nd-stage labor pain can be controlled satisfactorily by blocking the pudendal nerves or the first 3 sacral cord segments.

Types of Block.—Of the numerous regional technics used for 1st-stage labor pains, paracervical block is specific, in that it blocks only the pelvic (inferior hypogastric) ganglia and plexus. Continuous lumbar epidural anesthesia not only can block spinal cord segments T-11 and T-12 for 1st-stage labor pains, but the injection of more local anesthetic solution can extend the block to include the sacral segments for 2nd-stage labor pains. Therefore, lumbar epidural block is the preferred technic of many obstetric anesthesiologists.[26,27] Because of intense pain, it is common practice to initiate an analgesic technic during the 1st stage of labor. Because this stage may last up to 8 hours, analgesia must often be continued for many hours, with increased risk of fetal toxicity.

Paracervical block and continuous lumbar epidural block are the most commonly employed technics for 1st-stage labor pain.[26-30]

III. CLINICAL USE OF REGIONAL BLOCK

Paracervical Block. — Paracervical block with any agent is of potential danger to the fetus (table 2). The signs of fetal toxicity occur at a significant rate after block. Many studies have described the risk of fetal toxicity with this technic.

Paracervical Lidocaine. — Nyirjesy and colleagues[29] reported an incidence of 22 percent (15/68 cases) of fetal bradycardia after paracervical block with lidocaine. One fetal death occurred with a toxemic primagravida. Three minutes after the block, the

TABLE 2
Paracervical Block

Author	Cases	Drug	Dose, mg	Maternal, μg/ml	Fetus, μg/ml	pH	Bradycardia	Deaths
Nyirjesy[29]	68	Lidocaine 1%	200	ND*	ND	ND	15	1
Shnider and Gildea[31]	702	Prilocaine 1%	190-198	ND	ND	ND	77	
	356	Lidocaine 1%	190-198	ND	ND	ND	79	
	836	Mepivacaine 1%	190-198	ND	ND	ND	183	
Freeman[3]	92	Mepivacaine 1%	200	ND	ND	With bradycardia 10 min 7.19	24	
Teramo and Rajamaki[32]	5	Mepivacaine 1%	200	1.4-2.4	0.0-2.5	Decrease 0.01-0.07	0	
	1	Mepivacaine 1.5%	300	2.0-3.1	8.3	Decrease 0.16	1	
	6	Mepivacaine 2%	400	2.1-5.6	0.0-4.5	Decrease 0.03-0.15	5	
Rosefsky and Petersiel[18]		Mepivacaine 1.5%	300	ND	ND			1
		Mepivacaine 1.5%	240	ND	36 hr urine: 6.2; 45 hr urine: 0.75			1
	93	ND	ND	ND	ND	ND	43	
Baskett[5]	95	Bupivacaine 0.25%	50	ND	ND	ND	2	
		Lidocaine 1% with epinephrine 1:400,000	200	ND	ND	ND	1	
Teramo[34]	14	Bupivacaine 0.25%	50	ND	ND	Decrease 0.048		
	12	Bupivacaine 0.25% with epinephrine 1:200,000	50	ND	ND	Decrease 0.049		
	38						21	
	12	Bupivacaine 0.5% with epinephrine 1:200,000	100	ND	ND	Decrease 0.045		
Beck and Martin[37]	19,907	Bupivacaine 0.25%	50	ND	ND	ND		1
		Bupivacaine 0.5%	100	ND	ND	ND		30
	7887	Mepivacaine 1.0% or	200	ND	ND	ND		1
		mepivacaine 1.0% plus	100					
		bupivacaine 0.5%	50					

*ND = no data.

fetal heart tones disappeared. A stillbirth occurred 12 minutes after the application of the paracervical anesthetic.

Shnider and Gildea[31] describe bradycardia after paracervical blocks with prilocaine, lidocaine, or mepivacaine. In the fetuses with no signs of distress before anesthesia, there was an 18.1, 19.3, and 8.4 percent incidence of bradycardia after paracervical block with lidocaine, mepivacaine, and prilocaine, respectively. When there had been fetal distress prior to the paracervical block, bradycardia developed in 60 percent of the lidocaine, 44.7 percent of the mepivacaine, and 35.9 percent of the prilocaine blocks.

Paracervical Mepivacaine.—Freeman[3] reported a 26.1 percent incidence (24/92 cases) of fetal bradycardia following paracervical block with 200 mg of mepivacaine. Six of the 24 fetuses that developed bradycardia experienced the distress longer than 10 minutes and developed metabolic acidosis. The mean pH fell from 7.3 to 7.18 before returning slowly toward, but not reaching, baseline by 45 minutes. No deaths occurred in this series.

In a study[32] of the effects of mepivacaine paracervical blocks on 12 fetuses, 6 had bradycardia and a decrease of pH. Bradycardia did not develop in the fetuses whose mothers received a total of 200 mg of mepivacaine, but 1 fetus developed a pH decrease of 0.07 units. Five of the mothers received a 400 mg mepivacaine paracervical block, and the sixth received 300 mg. The fetal plasma concentration reached 8.3 μg/ml in the mother who received only 300 mg. The mean plasma concentration of the 6 fetuses with bradycardia was 3.07 (range 0.5 to 8.3) μg/ml. Those without distress had a lower mean plasma concentration (1.52 μg/ml), but the plasma concentration range (0.4 to 2.5 μg/ml) overlapped the values reported in the toxic group.

Rosefsky and Petersiel[18] reported 2 fetal deaths after paracervical blocks with 300 mg and 240 mg of mepivacaine. Six minutes after the 300 mg block, fetal heart rate decreased from 136 to 80. Eighty minutes later, fetal heart tones were lost. Ten minutes after the 240 mg block, fetal bradycardia of 80 bpm developed. At birth, the infant was flaccid; at 3 hours, the neonate developed opisthotonus; at 20 hours, seizures were present; and, at 45 hours, the infant died. Mepivacaine levels in the urine were 6.2 μg/ml at 36 hours and 0.75 μg/ml at death.

A recent report[33] describes 3 infants who manifested severe toxicity after maternal paracervical blocks with mepivacaine, 2 surviving with permanent neurologic damage following protracted convulsions and hypotonia. The third died after 7 days of life.

We reviewed the records of 23 parturients given mepivacaine block at our institution. The anesthetic technics included paracervical blocks, pudendal blocks, local infiltration, and 1 lumbar epidural block. There were detectable mepivacaine levels in the umbilical vein samples from 9 patients (39.1%). The cord mepivacaine levels were less than 1 μg/ml in 7 cases (30.4%). Five cases (21.7%) had mepivacaine levels ranging from 1 to 1.7 μg/ml. Three cases (13.4%) had toxic umbilical cord mepivacaine concentrations ranging from 2.5 to 9 μg/ml. The infant with a mepivacaine level of 2.5 μg/ml had been delivered under a paracervical followed 35 minutes later by a pudendal nerve block. The infant with 5 μg/ml of mepivacaine in the cord blood had been delivered with 2 paracervical blocks. The mother of the infant with an umbilical vein mepivacaine concentration of 9 μg/ml had received only a pudendal nerve block. The one recorded episode of bradycardia occurred after a paracervical block had been administered, but the cord mepivacaine level was only 1 μg/ml at birth. All 23 infants survived.

Paracervical Bupivacaine.—Baskett and Carson[5] observed bradycardia in only 3/95 cases after paracervical block. Two cases followed 50 mg of bupivacaine (the third occurred with 200 mg of lidocaine). Fetal heart tones were checked only at 15-minute intervals, which may explain the low incidence of bradycardia in this series.

Teramo[34] reported that 13/38 bupivacaine paracervical block cases developed fetal bradycardia of a moderate degree (100 to 118 bpm) and that 8 cases developed severe bradycardia (<100 bpm). The mean pH of the fetuses 2 minutes before the block was 7.351. After the block, the mean pH fell progressively 0.049 units at 15 minutes. By 40 minutes the pH value had returned toward the initial value but was still down 0.028 units. Also, there was a direct correlation between severity of bradycardia and the intensity of acidosis.

Paracervical block with bupivacaine has been associated with significant mortality. Whitehouse[35] reported on 25 cases of paracervical block with 0.5 percent bupivacaine

containing epinephrine 1:200,000. In 3 cases, 30 to 45 minutes after the paracervical blocks with 10 ml of the bupivacaine-epinephrine solution, significant bradycardia occurred. In 1 of these cases, fetal heart tones were lost, and a stillbirth was delivered 8 hours later. Other authors[36] reported that "several cases of extreme foetal bradycardia were seen following the injection of 2 x 10 ml of 0.5% bupivacaine into the paracervical space. . . ." One of these cases terminated in an intrauterine death within 20 minutes of the paracervical block.

In a retrospective study[37] of 32,652 cases of paracervical block from 107 German maternity units, bupivacaine was found to have been used in 19,907 cases. In 7887 cases, mepivacaine alone or in combination with bupivacaine was used. Fetal deaths occurred in 30 paracervical blocks with 20 ml of 0.5 percent bupivacaine, and 1 death was seen after 20 ml of 0.25 percent bupivacaine. One mortality followed in the 7887 cases of local anesthetic mixture, but other factors may have been responsible.

Epidural Lidocaine. — No deaths have been reported in any of the epidural lumbar series studied (table 3). Shnider[12] reported fetal toxicity from lidocaine, whether injected by the epidural, paracervical, pudendal, or caudal route. In a series of 57 patients, 3 groups were established. One group of 7 patients received single-dose caudal or lumbar epidural anesthesia. A second group of 27 patients had continuous caudal or lumbar epidural anesthesia. The other 23 patients had multiple-dose paracervical and pudendal blocks. The average lidocaine doses in these groups were 3 to 4.8 mg/kg, 8.19 mg/kg, and 5.6 mg/kg, respectively. Although the fetal toxicity was not given for each type of anesthesia, it was established that only 1 infant had a low Apgar score when the umbilical vein lidocaine concentration was <2.5 μg/ml. On the other hand, 4/8 infants had low 1-minute Apgar scores when the lidocaine concentration was >2.5 μg/ml. Two of these depressed infants had lidocaine levels of >3 μg/ml. No deaths were reported in this series.

Neonatal depression after maternal lumbar epidural anesthesia with lidocaine and mepivacaine has been described.[38] Of 32 infants in this series, 3, whose mothers had endured labor of 6, 9, and 9 hours, had 5-minute Apgar scores of 5 or less, requiring extensive resuscitation. The epidural anesthetics had required 625 mg of lidocaine, 975 mg of mepivacaine, and 950 mg

TALBE 3
Continuous Lumbar Epidural Block

Author	Cases	Drug	Dose/length of labor	Maternal, μg/ml	Fetus, μg/ml	Apgar	Bradycardia
Shnider and Way[14]	27	Lidocaine 1.5% with epinephrine 1:200,000	Single 2.9-10.1 μg/ml Multiple 3.0-14.2 μg/ml	<0.2-5.3 0.2-5.5	UV <0.2-1.6 0.4-3.4	Low when UV >2.5 μg/ml	
Lurie and Weiss[38]	13 19	Lidocaine Mepivacaine	625 mg/6 hr 975 mg/9 hr	2.2 2.2 average	2.32 2.31	≤5 ≤5	
Morishima[20]	19	Mepivacaine Mepivacaine 1.5% Single dose Intermittent doses	950 mg/9 hr 3.5-7.2 mg/kg 4.4-9.4 mg/kg	2.2 1.23 2.37-7.47	2.88 0.80 1.65-3.81	≤5 4 1-6	1 2
Thomas[22]	12	Bupivacaine 0.5% with epinephrine 1:200,000	50 mg/2⅔ hr 150 mg/8⅓ hr	At delivery 0.12-0.41	0.04-0.25	7-10	No toxicity
Reynolds and Taylor[41]	9	Bupivacaine 0.5% Bupivacaine 0.5% with epinephrine 1:200,000	60 mg/4 hr-250 mg/9¼ hr 60 mg/3 hr-210 mg/9½ hr	0.131-1.26 0.173-0.908	0.037-0.343 0.092-0.337		No toxicity

No deaths reported in these series.

of mepivacaine, respectively. Although the plasma concentration of mepivacaine in the mothers or depressed infants was not reported separately, the average maternal concentration from all mepivacaine epidural cases was 2.2 μg/ml, and the mean concentration of mepivacaine from all infants was 1.6 μg/ml. The dose range of administered lidocaine was 135 to 930 mg. The plasma concentrations were almost identical to those of the mepivacaine group. The maternal mean lidocaine concentration was 2.2 μg/ml and the neonatal plasma concentration was 1.55 μg/ml. Despite the low neonatal plasma concentrations, epidural anesthesia with either lidocaine or mepivacaine produced fetal toxicity.

Epidural Mepivacaine.—In a study of fetal depression caused by mepivacaine lumbar or caudal epidural anesthesia in 56 mothers,[20] 5 infants of 19 patients who received lumbar epidural anesthetics were depressed at birth, with Apgar scores of 6 or less (compared to 7/37 after caudal). These 5 infants were delivered after continuous anesthesia where mepivacaine dosage ranged from 4.4 to 9.4 mg/kg. The mepivacaine levels in the maternal blood ranged from 2.37 to 7.47 μg/ml. Fetal umbilical vein levels measured 1.65 to 3.81 μg/ml. The Apgar scores of these infants were 1, 2, 3, 6, and 6. The mother of the Apgar-1 infant had experienced mepivacaine toxicity with apprehension, nausea, and vomiting; her mepivacaine-blood concentration was 7.47 μg/ml, and the umbilical vein concentration was 3.81 μg/ml. There were no fetal or maternal complications in 1 of the 2 infants with an Apgar score of 6. The low Apgar scores of the other 3 infants resulted from either fetal or maternal complications not related to the anesthetic agent.

Although local anesthetics are not thought to show a substantial depression in concentrations below the toxic levels discussed above, neurologic and behavioral tests do show consistent changes in the babies born after epidural block. Standardized neonatal neurologic tests[39] have shown that babies born after epidural block have decreased muscular strength and tone during the first 8 hours of life. It has been suggested[40] that long-term investigations are needed to explore implications of these findings, for neonatal adjustment and maternal-neonatal relationships.

Although no direct comparisons can be made from the literature, the reported incidence of fetal toxicity after lidocaine or mepivacaine epidural anesthesia does not appear to offer any significant advantage over the toxicity associated with paracervical blocks with these agents. However, neonatal deaths appear to be uncommon after epidural anesthesia with either. The literature concerning bupivacaine appears to differ significantly.

Epidural Bupivacaine.—Continuous epidural anesthesia with bupivacaine has not been reported to be associated with maternal, fetal, or neonatal toxicity. In a description of 12 cases of bupivacaine epidurals,[22] the longest labor was 8¼ hours. Maternal plasma levels ranged from 0.22 to 0.61 μg/ml and umbilical venous plasma levels ranged from 0.25 to 0.94 μg/ml at birth. No maternal or fetal toxicity was observed, which is consistent with Jorfeldt's projected toxic bupivacaine levels (4 μg/ml for adults and 2 to 2.5 μg/ml for infants).[16]

In a study of maternal plasma concentrations after continuous lumbar epidural anesthesia in 18 parturients,[41] the maximal maternal plasma concentrations with 0.5 percent bupivacaine averaged 0.744 (range 0.45 to 1.33) μg/ml. The maximal mean level with 0.5 percent bupivacaine containing epinephrine 1:200,000 was 0.555 (range 0.388 to 0.908) μg/ml. Umbilical-vein concentrations were 0.037 to 0.343 (mean 0.161) μg/ml for 0.5 percent bupivacaine and 0.092 to 0.337 (mean 0.18) μg/ml for 0.5 percent bupivacaine with epinephrine 1:200,000, epinephrine lowering the maximal maternal plasma concentration but slightly increasing neonatal blood concentration. No toxicity was observed in this study, neither the maternal nor the fetal plasma bupivacaine levels approaching the projected toxic levels.

Thomas' 12 cases[22] and Reynolds' 18 cases[41] represent small series. Crawford,[42] however, reported on 1000 cases, in which all complications were attributed either to the procedure (inadvertent subarachnoid taps, etc) or to the block but none to bupivacaine toxicity. Although he did not specifically comment upon fetal or neonatal depression, apparently no neonatal deaths occurred in this series.

CONCLUSIONS

The longer duration of action and lower effective total dose of bupivacaine appear to make this agent the amide of choice for continuous lumbar epidural anesthesia. Paracervical block is a hazardous technic; if

it must be used, careful attention must be paid to total dose of the drug, avoidance of intravascular injection, and evidence of fetal distress prior to block. Placental insufficiency and prematurity are absolute contraindications to paracervical block, according to Shnider.[43]

Although bupivacaine does not appear to offer any advantage over the other amide agents for paracervical block, the ester class of local anesthetics appear to offer definite advantages in terms of blood levels achieved and toxic manifestations. Local block with the ester anesthetics is reportedly effective for at least 1¼ hours; therefore, these anesthetics would appear to be the agents of choice within 1 hour of delivery for any block. The relative safety and efficacy of the ester versus amide anesthetics should be carefully considered whenever a choice between paracervical, pudendal and local block is to be made. In addition, the relative efficacy and toxicity of bupivacaine for continuous epidural blocks should continue to be studied.

REFERENCES

1. Bromage PR, Robson JG: Concentrations of lignocaine in the blood after intravenous, intramuscular, epidural, and endotracheal administration. Anaesthesia 16:461-478, 1961

2. Moore DC: Continuous (intermittent) epidural (peridural) block, Regional Block. Springfield, Illinois, Charles C Thomas, Publisher, 1971

3. Freeman RK, Gutierrez NA, Ray ML, et al: Fetal cardiac response to paracervical block anesthesia (part I). Am J Obstet Gynecol 113:583-591, 1972

4. DeKoninck J, Goodrich RW Jr: Paracervical block in obstetrics: an evaluation of various anesthetic agents. Conn Med 29:182-184, 1965

5. Baskett TF, Carson RM: Paracervical block with bupivacaine. Can Med Assoc J 110:1363-1365, 1974

6. Gudgeon DH: Paracervical block with bupivacaine 0.25%. Br Med J 2:403, 1968

7. Levinson G, Shnider SM: Placental transfer of local anesthetics: clinical implications. Clin Anesth 10:174-185, 1973

8. Weiss CF, Glazko AJ, Weston JK: Chloramphenicol in the newborn infant. N Engl J Med 262:787-794, 1960

9. Yaffe SJ, Rane A, Sjoquist F, et al: The presence of a mono-oxygenase system in human fetal liver microsomes. Life Sci 9:1189-1200, 1970

10. Meffin P, Long GJ, Thomas J: Clearance and metabolism of mepivacaine in the human neonate. Clin Pharmacol Ther 14:218-225, 1972

11. Ostheimer GW, Lurie AO, Brown WV, et al: Maternal and newborn concentrations of bupivacaine and 2.6 pipercoloxylidide (PPX) in blood and urine. American Society of Anesthesiologists Annual Meeting, Abstracts of Scientific Papers, 1974

12. Shnider SM, Way EL: Plasma levels of lidocaine (Xylocaine®) in mother and baby following obstetrical conduction anesthesia. Anesthesiology 29:951-958, 1968

13. Widdas WF: Transport mechanisms in the fetus. Br Med Bull 17:107-111, 1961

14. Tucker GT, Boyes RN, Bridenbaugh PO, et al: Binding of anilide-type anesthetics in human plasma: 1. Relationships between binding, physicochemical properties, and anesthetic activity. Anesthesiology 33:287-302, 1970

15. Foldes FF, Mollow MB, McNall PG, et al: Comparison of toxicity of intravenously given local anesthetic agents in man. JAMA 172:1493-1498, 1960

16. Jorfeldt L, Lofstrom B, Pernow B, et al: The effect of local anaesthetics on the central circulation and respiration in man and dog. Acta Anaesthesiol Scand 12:153-169, 1968

17. Heymann MA: Effects of local anesthetic agents on the fetal circulation, Perinatal Pharmacology: Problems and Priorities. Edited by J Dancis, JC Hwang. New York, Raven Press, 1974

18. Rosefsky JB, Petersiel ME: Perinatal deaths associated with mepivacaine paracervical-block anesthesia in labor. N Engl J Med 278:530-533, 1968

19. Gunther RE, Bauman J: Mepivacaine compared with lidocaine for obstetrical anesthesia. Anesthesiology 31:5-8, 1969

20. Morishima HO, Salha SD, Mieczyslaw F, et al: Transmission of mepivacaine hydrochloride (Carbocaine) across the human placenta. Anesthesiology 27:147-154, 1966

21. Martin K, Rathgen GH, Schwethelm R, et al: Mepivacain (Scandicain) Blutspiegeluntersuchungen nach Parazervikalenblock. Geburtshilfe Frauenheilkd 29:711, 1969

22. Thomas J, Climie CR, Mathes LE: The maternal plasma levels and placental transfer of bupivacaine following epidural analgesia. Br J Anaesth 41:1035-1040, 1969

23. Teramo K, Widholm O: Effects of obstetrical paracervical blockade on the fetus. Acta Obstet Gynecol Scand 16 (Suppl):39-43, 1967

24. Jung H, Kopecky P, Klock FK: Die fetale Gefahrdring durch die Parazervikalblockaden. Geburtshilfe Frauenheilkd 29:519, 1969

25. Wagman IH, deJong RH, Prince DA: Effects of lidocaine on the CNS. Anesthesiology 28:155-167, 1967

26. Moir DD: Recent advances in pain relief in childbirth. II: Regional anaesthesia. Br J Anaesth 43:849-860, 1971

27. Shnider SM, Experience with regional anesthesia for vaginal delivery. The Anesthesiologist, Mother and New Born. Shnider, S M and Moya F (eds). Baltimore, The Williams & Wilkins Company, 1974, chapter 4, p 39

28. Gordon HR: Fetal bradycardia after paracervical block. Correlation with fetal and maternal blood levels of local anesthetic (mepivacaine). N Engl J Med 279:910-914, 1968

29. Nyirjesy I, Hawks BL, Hebert JE, et al: Hazards of the use of paracervical block anesthesia in obstetrics. Am J Obstet Gynecol 87:235-237, 1963

30. Burt RAP: The foetal and maternal pharmacology of some of the drugs used for the relief of pain in labour. Br J Anaesth 43:824-833, 1971

31. Shnider SM, Gildea J: Paracervical block anesthesia in obstetrics. III. Fetal bradycardia following administration of lidocaine, mepivacaine, or prilocaine. Am J Obstet Gynecol 116:320-325, 1973

32. Teramo K, Rajamaki A: Foetal and maternal levels of mepivacaine and foetal acid-base balance and heart rate after paracervical block during labour. Br J Anaesth 43:300-311, 1971

33. Hales SW, Daily WJR, Meyer HBP: Mepivacaine toxicity in the neonate. Clin Res 23:158A, 1975

34. Teramo K: Fetal acid-base balance and heart rate during labor with bupivacaine paracervical block anesthesia. J Obstet Gynaecol Br Commonw 76: 881-885, 1969

35. Whitehouse DB: Paracervical block with bupivacaine. Br Med J 2:764, 1968

36. Ruoss C, Beasley JM: Paracervical block with bupivacaine. Br Med J 2:622-623, 1968

37. Beck L, Martin K: Hazards associated with paracervical block in obstetrics. Ger Med Mon 15:81-83, 1970

38. Lurie AO, Weiss JB: Blood concentration of mepivacaine and lidocaine in mother and baby after epidural anesthesia. Am J Obstet Gynecol 106:850-855, 1970

39. Scanlon JW, Brown WV Jr, Weiss JB, et al: Neurobehavioral responses of newborn infants after maternal epidural anesthesia. Anesthesiology 40: 121-128, 1974

40. Editorial: Obstetric analgesia and the newborn baby. Lancet 1:1090, 1974

41. Reynolds R, Taylor G: Plasma concentrations of bupivacaine during continuous epidural anaesthesia in labour: the effect of adrenaline. Br J Anaesth 43:436-439, 1971

42. Crawford JS: Observations on one thousand epidural blocks given in labour, Proceedings from the Symposium on Epidural Analgesia in Obstetrics. Edited by A Doughty. 1971, pp 83-90

43. Shnider SM, Asling JH, Holl JW, et al: Paracervical block anesthesia in obstetrics: 1. Fetal complications and neonatal morbidity. Am J Obstet Gynecol 107:619-625, 1970

CORRECTION

Estimation of Anesthetic Solubility in Blood—Feingold.

The formula appearing on page 595, Brief Reports Section of the July-August 1976 issue should read: $B/G = 0.89\ W/G + 0.011\ F/G$ (III)

Obstetric Anesthesia Training Centers in the U.S.A.—1975

JAMES S. HICKS, MD*
GERSHON LEVINSON, MD†
SOL M. SHNIDER, MD‡
San Francisco, California§

The current status of obstetric anesthesia training in the United States is reviewed. The 39 anesthesia residency training programs having full time chiefs of obstetric anesthesia were surveyed regarding clinical practice, physical facilities, teaching and research. This paper reports the results and compares them to recommendations of JCAH, ACOG and ASA, concerning standards of patient care and resident teaching.

THE training of personnel to provide obstetric anesthesia and the provision of this care to patients are continuing problems. Of the 171 approved anesthesia residency training programs in the United States, 39 have full-time chiefs of obstetric anesthesia. Presumably the teaching, research, clinical practice, and physical facilities for labor, delivery, and neonatal care at these centers would be of highest quality and may serve as models for all hospitals providing maternity care. The present study evaluates their compliance with recommendations of the Joint Commission on Accreditation of Hospitals (JCAH),[1] American College of Obstetrics and Gynecology (ACOG),[2,3] and American Society of Anesthesiologists (ASA),[4,5] and how they have dealt with weaknesses previously identified by ACOG[6] and by Shnider.[7]

METHOD

In 1974 and 1975, with the assistance of the Society of Obstetric Anesthesia and Perinatology, 39 chiefs of obstetric anesthesia responded to questionnaires designed to determine:

1. The professional category of the personnel administering obstetric anesthesia;
2. The amount of faculty supervision;
3. The type of anesthesia used for vaginal delivery and cesarean section;
4. The physical facilities in the labor and delivery room and neonatal intensive care unit (ICU);
5. The methods, amount, and scope of teaching obstetric anesthesia to anesthesia, obstetric, and pediatric residents and nurse anesthetists (RNA);
6. The extent of research currently conducted in obstetric anesthesia and source of funding for research.

RESULTS*

Geographic distribution of the programs surveyed represents 22 states and the District of Columbia. Twelve centers are in the East, 9 Southeast, 5 Midwest, 2 Southwest, and 11 Far West. All have both obstetric and anesthesiologic training programs and 3

*Unless otherwise defined, percentages refer to hospitals.

*Research Fellow.
†Assistant Professor of Anesthesia, Obstetrics and Gynecology.
‡Professor of Anesthesia, Obstetrics and Gynecology.
§Departments of Anesthesia, Obstetrics and Gynecology, University of California, San Francisco, California 94143.

This study was supported in part by USPHS Anesthesia Research Center 5 P01 GM 15571-8.

Reprint requests to Dr. Shnider.

Paper received: 1/9/76
Accepted for publication: 2/24/76

are military hospitals. The total births per year among the hospitals is 121,210 (3% of the national births) with a mean of 3190 (range 650 to 10,800). Of the 1376 anesthesia residents in the USA, 711 train in these hospitals. An average of 2 residents are assigned to obstetric anesthesia at any one time.

Since perinatology encompasses aspects of anesthesia, obstetrics, and pediatrics, we queried directors as to the organization of their departments. Five of the 39 (13%) employ a chairman of perinatal medicine overseeing parts of all 3 disciplines; 32 (82%) have conventionally organized departments, and 2 (5%) report other unspecified structures.

Clinical Practice.—Anesthesiologists give 56 percent of anesthetics; obstetricians, 32 percent; and RNAs, 10 percent. Three-quarters of patients delivering vaginally receive regional anesthesia, primarily pudendal nerve blocks, lumbar epidurals, and low spinals ("saddle-block") (table 1). Only 6 percent of such patients receive caudal anesthesia (1-shot or continuous). General anesthesia is used in only 6 percent, and an endotracheal tube is placed in 2/3 of these cases. Lamaze or other psychoprophylactic technics are elected by 10 percent of the patients, with analgesic supplementation required in 60 percent of these.

TABLE 1
Type of Anesthesia for Vaginal Delivery

Anesthesia technic	Percent of total deliveries*
Minor regional	
Pudendal block	26
Psychoprophylaxis	
Lamaze—with supplement	6
without supplement	4
Major regional	
Lumbar epidural—continuous	24
Saddle block	21
Caudal—continuous	5
one shot	1
Inhalation	
Inhalation analgesia	13
General anesthesia—endotracheal tube	4
General anesthesia—mask	2

*Does not add up to 100 percent because some patients had 2 technics, eg, pudendal and inhalation analgesia.

TABLE 2
Cesarean Sections Classified by Type of Anesthesia Used

	Percent of cesarean sections	
	All maternity units*	Obstetrical anesthesia centers
Spinal	53	24
Inhalation	32	43
Combination	9	—
Epidural	3	32
Local	1	1
Other	1	—

*ACOG Survey 1970.[6]

The cesarean section rate is 10.6 (range 7 to 20) percent. Conduction anesthesia is most frequently used, with epidurals more popular than spinals (table 2). General anesthesia is used in 43 percent of cases.

In at least 69 percent of the hospitals, patients with epidural blocks started during labor always are monitored by a physician, while in the other hospitals, RNs or RNAs monitor them. A physician or RN provides continuous patient care in 59 percent, but in 20 percent, the patient is monitored for less than 30 minutes after block (table 3).

Despite severe fetal complications described after paracervical block (PCB),[8] 80 percent of respondents use PCB occasionally to control pain during the 1st stage of labor. Fetal heart rate (FHR) changes always are monitored following the block. In half the hospitals, FHR is continuously monitored electronically, and in half by

TABLE 3
How Long Does Someone Stay with Patient After Block?

Length of time	Percent of hospitals
5 minutes*	5
15 minutes*	5
20 minutes*	10
30 minutes*	13
60 minutes*	3
Greater than 60 minutes but not continuous	5
Continuous	59
	100

*With variable intermittent rechecks.

TABLE 4
Antepartum Education of Parents

	Percent of hospitals		
	Yes	Sometimes	No
Are mothers interviewed during pregnancy by an anesthesia department representative?	5	18	77
Are mothers given any literature regarding alternatives of anesthesia?	24	—	76
Do mothers (and fathers) tour the OB suite during pregnancy?	54	18	28
Do they see films or other audio or visual aids concerning:			
Management of common problems during pregnancy?	54	20	26
Normal vaginal delivery?	51	16	33
Choice of anesthesia?	49	10	41
Is Lamaze instruction available?	82	—	18
Is it coordinated with the hospital?	71	—	29

auscultation at varying intervals for 5 to 20 minutes after block.

In half the hospitals, obstetricians administer major conduction anesthesia, accounting for 19 percent of the total blocks. In 10 percent, RNAs administer regional anesthesia, but only a small fraction (2%) of the total number of blocks performed.

Antepartum education of mothers and fathers to reduce anxiety and establish rapport with the staff is an important aspect of contemporary obstetrics. Although most expectant mothers and often fathers tour the obstetric suite during the antepartum period, in 3/4 of the hospitals, the anesthesia department plays no role in these activities (table 4). Lamaze instruction is available to the patients in 82 percent. In 55 percent, preanesthetic evaluation of the parturient is immediate on arrival at the hospital; in 45 percent, evaluation is just before anesthesia administration.

Physical Facilities.—Each hospital has an average of 6 labor rooms, giving a ratio of 0.7 labor rooms/delivery/day. Only 1 respondent reports use of a combined labor/delivery room, but another 7 (17%) plan to incorporate this feature in future construction or remodeling plans.

In almost all hospitals, the labor suite possesses emergency resuscitation equipment, and in over half, O_2, suction equipment, and a resuscitator bag are kept in each labor room. In 85 percent, cesarean sections can be performed in each delivery room. While ECG monitors are available in 3/4 of the delivery suites, less than 1/5 have automatic blood pressure monitors.

The immediate availability of blood products is of particular concern to the obstetric anesthesiologist. Fifteen percent report that low-titer Rh-negative type O whole blood or packed cells are always available in the delivery room and in 95 percent, a blood bank is an average of 6 minutes away.

Three-quarters of the hospitals can continuously record FHR and intrauterine pressure in each labor room. All can monitor these variables in selected patients. The overall patient-monitoring rate is 42 percent. Fetal scalp blood sampling is available in 31/39 centers (79%). Facilities for blood-gas analysis exist in 56 percent of the obstetric suites.

Seventy-nine percent of hospitals have an independent obstetric recovery room, while 10 percent use the surgical recovery room. However, only 13/31 centers with obstetric recovery rooms employ specially trained recovery-room nurses.

Adjacent to the delivery rooms, 23 percent have an area designed for intensive neonatal resuscitation. Each hospital has a distinct intensive care nursery (ICN), 36 percent of which are located near the obstetric suite. Twenty-one percent have a full-time neonatal anesthesiologist and 82 percent have at least 1 full-time pediatric neonatologist. The neonate:nurse staffing ratios in these well-equipped units vary from 1:1 to 4:1 (table 5).

TABLE 5
Neonate to Nurse Ratio in ICN

Ratio	Percent of hospitals
1 to 1	18
1 to 1 for very ill 2 or 3 to 1 for others	24
2 to 1 or 3 to 2	34
3 to 1	11
4 to 1 or greater	13
	100

TABLE 6
Conferences and Lectures

Conference title	Median frequency	Percent of hospitals not having conferences
Case review	Weekly	12
Perinatal morbidity and mortality	Monthly	18
Anesthesia morbidity and mortality	Weekly	9
High risk pregnancy	Monthly	40
Infant resuscitation	Monthly	24
Obstetric grand rounds	Weekly	19

Teaching.—In addition to the chief, 70 percent of the hospitals use an additional 1 or 2 faculty members to teach obstetric anesthesia. Faculty anesthesiologists are present at all times in 31 percent of the hospitals and in 85 percent, the faculty take both obstetric and surgical-anesthesia call nights and weekends.

In 18 (46%) programs, over half the anesthetics administered for vaginal delivery are directly supervised by faculty anesthesiologists. In 34 (88%) programs, more than half the anesthetics for cesarean sections are directly supervised by the faculty. In 18/39 centers, every anesthetic for cesarean section is supervised by a faculty anesthesiologist.

Teaching sessions, composed of formal lectures and informal rounds, vary widely (table 6). Two-thirds of the hospitals conduct at least weekly case-review conferences; 3/4 hold at least monthly perinatal morbidity-mortality conferences, and 1/2 conduct at least monthly infant-resuscitation seminars.

Obstetric residents rotate through the obstetric anesthesia service in 51 percent, and these residents also rotate through the surgical anesthesia service in 31 percent. Rarely are pediatric residents assigned to anesthesia: they rotate through the obstetric anesthesia service in 8 percent and also through the surgical anesthesia service in 3 percent. Anesthesia residents rotate to the neonatal nursery in 21 percent and to obstetrics in 5 percent.

Thirteen centers train RNAs in obstetric anesthesia. The majority teach administration of general anesthesia and the monitoring of regional blocks. Five teach spinal and epidural anesthesia.

Research. — Three-quarters of the programs include research of some type: 29 pursue clinical studies while 14 also perform animal research. The most common source of funding research is the drug industry (44%). Thirty-two percent of the programs receive NIH support, while 24 percent receive money from their schools of medicine.

Only 10 centers currently have a clinical or research trainee (total, 21 trainees) in obstetric anesthesia, although 37 openings are currently available. Two-thirds of the chiefs believe that research experience should be required of all residents planning careers in obstetric anesthesia.

DISCUSSION

The 39 hospitals surveyed represent a small fraction of the 5000 obstetric services in the United States.[6] However, they are responsible for the major proportion of residency training in obstetric anesthesia, and presumably the practice in these centers eventually will be reflected throughout American obstetrics.

While the mean delivery rate at these hospitals is 3190/year, 13 have fewer than 2000 and 23 have fewer than 3000 deliveries/year. A minimum of 2000 to 3000 deliveries/year probably is necessary to support round-the-clock coverage and teaching in obstetric anesthesia as well as ancillary services such as neonatal intensive care.[7,9] Smaller units likely are subsidized by the hospital or anesthesia departments to provide training in obstetric anesthesia and optimal care for parturient and neonate. This situation obviously is not ideal, and hopefully efforts will be made to merge these units with others in the community to create larger maternity and child-health centers.

The JCAH requires that "the same competence of anesthesia personnel shall be available for obstetrical . . . procedures as is available for elective procedures."[1] Two surveys of all American maternity units[6,10] published in 1970 and 1962, respectively, showed that anesthesiologists administer a minor percentage of total anesthetics for vaginal delivery (table 7), RNAs and obstetricians administering most of the anesthetics. This has been attributed to problems of manpower, economics, and motivation.[11] In the centers, where these factors are not as significant, anesthesiologists do provide most anesthesia (table 7).

While it appears that obstetricians are

TABLE 7
Category of Personnel Administering Anesthesia for Vaginal Delivery Most of Time

	Total maternity units USA		Obstetrical anesthesia centers
	1962*	1970†	1975
Anesthesiologist	15	12	61
CRNA	31	25	5
Obstetrician	26	34	31
RN, house staff, others	28	18	3

*Phillips and Frazier.[10]
†ACOG survey.[6]

administering an inordinately large percentage of the anesthetics for vaginal delivery, the majority of these are pudendal nerve blocks, minor regional procedures not performed by anesthesia personnel (table 1). If all parturients, nationwide, were to receive the same anesthesia coverage as those in the centers, anesthesiologists would administer anesthesia to 2/3 of the 3 million annual deliveries. Such optimal obstetric anesthesia is not feasible without a major consolidation of maternity units and unless more anesthesiologists join in obstetric units.

For the foreseeable future, obstetricians and RNAs must provide the major share of obstetric anesthesia. In 1/3 of the hospitals nationwide, obstetricians do most of the anesthesia for vaginal delivery. The Council on Resident Education in Obstetrics and Gynecology (CREOG), an intersociety organization founded to improve all aspects of residency training in obstetrics and gynecology, believes that all obstetricians should possess skill in using common anesthetic and analgesic technics, including local infiltration, spinal, epidural, and general anesthesia.[12]

Accordingly, ACOG has recommended[13] that all obstetric residents receive organized instruction for 2 or 3 months in anesthesia technics and management of anesthetic complications. Shnider's 1965 survey[14] showed that 49 percent of obstetric residents received no formal instruction in obstetric anesthesia from an anesthesiologist. Our present survey indicates little progress. Again, only about half the residents in obstetrics receive training in a department of anesthesia. Increased efforts in this area are essential.

We believe that although a 2-to-3 month period of anesthesia training is a desirable aspect of an obstetrical residency, this length of time is insufficient to accomplish the CREOG aims. We endorse the 1974 ACOG standards:[3]

"Whenever possible, obstetric anesthesia should be supervised by a qualified anesthesiologist, and administered by an anesthesiologist or a certified registered nurse anesthetist. It is further recommended that the safest methods for the obstetrician himself to use, when the above personnel are not available, are infiltration anesthesias such as local block, paracervical block, or pudendal block."

In 25 percent of American maternity hospitals, RNAs administer most anesthetics for vaginal delivery.[6] They primarily administer inhalation anesthesia and analgesia and monitor but never administer a major regional anesthetic.[10] Regional anesthesia is preferred for vaginal delivery in the 39 units we surveyed. At present, only 5 centers, 3 of which are in military hospitals, train RNAs to administer major conduction anesthesia. Should not more RNAs be trained to do regional blocks under supervision? The obstetric anesthesia centers would be logical sites for such training.

The anesthesia used in the centers differs from that used in most other American maternity units. This reflects both the availability of fully trained obstetric anesthesiologists and also their belief as to the best anesthetic technics. For example, ACOG (table 8) found that the majority of vaginal deliveries were conducted under inhalation anesthesia in 36 percent of maternity units,

TABLE 8
Percent of Hospitals Classified by Type of Anesthesia Most Often Used for Vaginal Delivery

Type of anesthesia	All maternity* units, percent	Obstetrical anesthesia centers, percent
Inhalation	36	0
Local and pudendal	16	33†
Spinal and epidural	14	57‡
Other	12	5
No predominant type	22	5

*ACOG Survey 1970.[6]
†Often includes inhalation *analgesia.*
‡57% = 31% saddle; 21% epidural; 5% caudal.

but in no center is inhalation anesthesia the most popular technic; only 6 percent of vaginal deliveries were conducted under general anesthesia (table 1), and we believe obstetric indications necessitated this use. It is noteworthy that 2/3 of these patients had endotracheal intubation to protect them from aspiration pneumonitis.

The majority of vaginal deliveries are conducted under spinal or epidural anesthesia in only 14 percent of American hospitals but in 57 percent of the centers (table 8). Most patients in the centers receive major regional anesthesia (table 1), the most popular technic being continuous lumbar epidural anesthesia. Caudal epidural blocks, long popular in obstetrics and considered by many authorities one of the best methods of obstetric anesthesia,[15] are used only in 6 percent of deliveries.

Patients who receive continuous epidurals must be carefully monitored by trained personnel. The ACOG technical bulletin[2] recommends measurement of blood pressure at least every 2 minutes for the first 10 minutes and then at least every 5 minutes for the next 20 minutes after anesthetic injection. This is a minimum standard, considering the constant supervision a surgical patient receives following an epidural block in the operating room, but even this recommendation is not followed in 20 percent of the centers (table 3).

Despite widespread publicity and the availability of Lamaze instruction (82% of centers), only 10 percent of parturients use this technic, and the majority of these require some form of supplementary analgesia. This suggests that psychoprophylaxis should not be depended upon to replace conventional obstetric anesthesia.

Ideally, an anesthesiologist should see each parturient either individually or in a group setting as part of antepartum orientation and education, to establish rapport with the patient and describe the risks and benefits of the various types of anesthesia available. Yet in only 5 percent of centers are mothers interviewed during the antepartum period. Failing such an antepartum opportunity, an intrapartum, unhurried preanesthetic evaluation and discussion of anesthesia should be performed immediately on the parturient's arrival in the delivery suite. Unfortunately, in half the hospitals an anesthesiologist does not see the patient until *immediately* prior to administration of anesthesia.

Within the centers, the popularity of epidural anesthesia for cesarean section is striking. Whereas the ACOG study of all maternity units showed that epidural anesthesia was used in only 3 percent of cesarean sections, in the centers it is used in 32 percent. Both groups use conduction anesthesia with similar frequency for cesarean section, but spinal is less popular within the centers (table 2). We speculate that although the onset of anesthesia is more rapid with spinal, department chiefs prefer the slower onset and more controllable anesthetic levels and cardiovascular alterations with epidural blocks.

Perinatology.—Progress toward a multitrained specialist in perinatology is slow. Only 13 percent of the centers have a combined perinatology service, 8 percent of the hospitals have pediatric residents rotate in obstetric anesthesia, and 21 percent have anesthesia residents rotate to the neonatal nursery. Whether perinatology as a distinct specialty represents a discipline of the future is not clear. Physicians still attach great significance to the concept of the "fully trained" specialist. Whether there can exist a "perinatologist" who is obstetrician but not gynecologist, obstetric but not surgical anesthesiologist, and neonatologist but not general pediatrician is speculative. At present, the majority of the centers have combined interdisciplinary conferences and seminars. Surprisingly, a quarter of the centers have no conferences on infant resuscitation.

Equipment and ICUs.—JCAH requires, and ASA and ACOG recommend, that equipment for the obstetric patient equal that available for surgical patients.[1-3] Most centers comply with these recommendations. Virtually every delivery room has an anesthesia machine, wall suction, piped O_2, and infant resuscitator. In 85 percent of the hospitals, cesareans can be performed in *each* delivery room. In contrast, a quarter of the nationwide hospitals surveyed by ACOG required *more than 40 minutes* to prepare for an emergency cesarean.

While each center has a well-equipped neonatal ICU, only 23 percent have an area immediately adjacent to the delivery room for major resuscitation of the premature or severely asphyxiated newborn. Such an area is indispensible in minimizing the delay between delivery and the institution of definitive resuscitation.

ICU staffing in the centers is generally good, with 82 percent having at least 1 full-time neonatologist. However, the neonate:

nurse ratio is not ideal; in only 42 percent is a very ill neonate attended by a nurse at all times, and in only 72 percent is the ratio of 1 nurse to 2 neonates observed.

CONCLUSIONS

Between 250 and 400 major referral centers for obstetric and neonatal problems ("Level III" facilities) will be necessary to provide optimal maternal and neonatal care in the USA.[16] A group of concerned organizations represented in the Committee on Perinatal Health has produced the following recommendations for such centers:

"Anesthesia services *must* be directed by an anesthesiologist with special training in maternal-fetal and neonatal anesthesia. . . ."

Obstetric anesthesia centers must assume responsibility for this special training in addition to their routine training of obstetricians and anesthesiologists.

Currently, 75 percent of these centers do not have a clinical or research trainee in obstetrical anesthesia either because of lack of funds or qualified or interested candidates. If the modest goals of the Committee on Perinatal Health are to be attained, significant increases in financial support, training facilities and personnel must be forthcoming.

REFERENCES

1. Joint Commission on Accreditation of Hospitals: Accreditation Manual for Hospitals. Chicago, 1970 (updated 1973)

2. American College of Obstetricians and Gynecologists: Obstetric Analgesia and Anesthesia, ACOG Technical Bulletin #11. Chicago, revised October 1973

3. American College of Obstetricians and Gynecologists: Standards for Obstetric-Gynecologic Services. Chicago, 1974

4. American Society of Anesthesiologists, Maternal Welfare Committee: Training in Obstetrical Anesthesia for Anesthesiology Residents. Annual Report, Enclosure 2, 1964

5. American Society of Anesthesiologists: Handbook of Hospital Facilities. Edited by JT Martin. Park Ridge, Illinois, Second edition, 1974, pp 179-181

6. American College of Obstetricians and Gynecologists. A Report of the Committee on Maternal Health: National Study of Maternity Care. Survey of Obstetric Practice and Associated Services in the Hospitals in the United States. Chicago, 1970

7. Shnider SM: Obstetric anesthesia coverage: problems and solutions. Obstet Gynecol 34:615-620, 1969

8. Shnider SM, Asling JH, Holl JW, et al: Paracervical block anesthesia in obstetrics. I. Fetal complications and neonatal morbidity. Am J Obstet Gynecol 107:619-625, 1970

9. Hehre FW: Observations philosophic and opinionated on obstetric anesthesia coverage, Public Health Aspects of Critical Care Medicine and Anesthesiology. Edited by P Safar. Philadelphia, FA Davis Company, 1974, vol 10/3, pp 323-333

10. Phillips OC, Frazier RM: Obstetric anesthesia care in the United States. Obstet Gynecol 19: 796-802, 1962

11. Churchill-Davidson H: Introduction to symposium on obstetrical analgesia and anaesthesia. Acta Anaesthesiol Scand Suppl 25:343-402, 1966

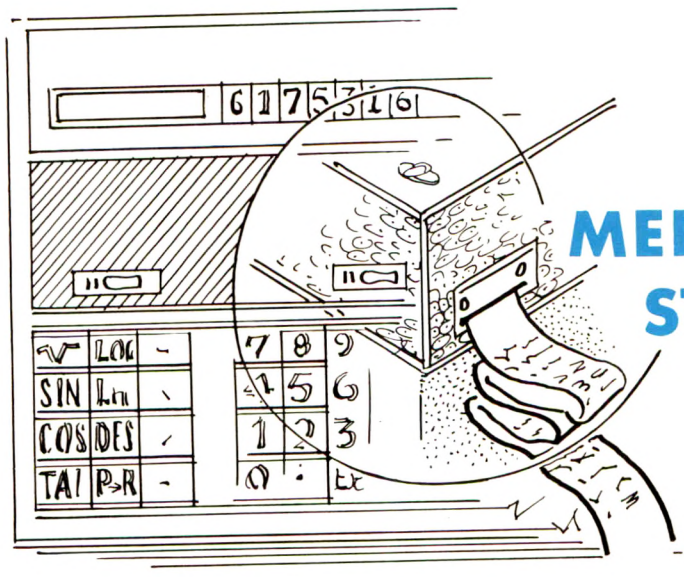
12. Council on Resident Education in Obstetrics and Gynecology: Contents of a Residency in Obstetrics and Gynecology. Chicago, 1974

13. American Society of Anesthesiologists, Maternal Welfare Committee: Anesthesia Training for Obstetrical Residents. Annual Report, Enclosure 3, 1964

14. Shnider SM: Training in obstetric anesthesia in the United States. Am J Obstet Gynecol 93:243-252, 1965

15. Bonica JJ: Principles and Practice of Obstetric Analgesia and Anesthesia. Philadelphia, FA Davis Company, 1967, chapter 35, p 574

16. Russell KP, Gardiner SH, Nichols EE: A conceptual model for regionalization and consolidation of obstetric-gynecologic services. Am J Obstet Gynecol 121:756-764, 1975



MEDICAL STATISTICS

Statistical Pearls III. The Most Likely Interpretation

PATRICK D. HARRIS, PhD*

PROBABILITY is probably the most important word in modern biomedical research. Yet, it would be difficult for most of us to answer the question, "What is probability?" In a sense, probability is like a pregnant woman in that it is a currently existing condition which defines an *expected* future event. Probability is a prediction of the *future*, but our *measure* of probability comes from past observations. The more information we have about past events, the better is our prediction of a future possibility.

Recently, a colleague, D. L. Wiegman, brought me some interesting data which involved one interpretation of probability. Essentially, he had used a well-defined protocol to hemorrhage rats for 1 hour. He had records of body weight (grams) at the time of hemorrhage and death (d) or survival (s) for the 24-hour period which followed reinfusion of the hemorrhaged volume. These data were: 166/s, 196/d, 146/d, 191/s, 204/s, 153/d, 208/d, 206/s, 220/d, 119/d, 185/s, 175/s, 151/d, 140/s, 140/d, 139/d, 179/s, 158/d, 161/s, 143/s, 155/d, 144/d, 145/s, 180/s, 196/s, 172/s, 172/s, 112/d, 159/s, 120/d, 115/d, 116/s, 127/d, 155/d, 117/s, 110/d, 114/s, 150/s. The average weight was 156 gm, with a range from 110 to 220 gm and survival was 52.6 percent (20sX100/38). At this point, one might predict that any future rat would have a 52.6 percent probability of being alive 24 hours after hemorrhage with the protocol. Is this a good prediction regardless of the weight of this future rat?

An investigator might attempt to answer this question by construction of a histogram[1] for the existing data. One such attempt would give a histogram with "percent survival in each weight class" on the

*Investigator, Dalton Research Center; Associate Professor of Physiology, University of Missouri School of Medicine, Columbia, Missouri 65201.

ordinate and with "body weight in grams" on the abscissa. The abscissa would be divided into 8 class intervals with a starting point of 100 gm and with an interval size of 15 gm. This histogram would be difficult to interpret, however, because 6 of the intervals would contain 5 or less observations (animals).

For the individual weight/survival data above, we posed the question, "Is the probability for survival independent of body weight (ie, the same for weights between 110 and 220 gm)?" We will approach the answer to this question by use of a *cumulative distribution* curve (fig 1). For our data, the abscissa is expressed as "body weight in grams" with "steps" which are *as small as* possible. Ideally, we should have *one* observation for each abscissa step from the smallest weight to the largest weight, so we have selected a 3-gm step size (approximately [200-110]/38). The first step is selected by the formula: the "largest weight" (220 gm) minus the product of the "step size" (3) and the "number of observations less one" (38 − 1). Thus, our starting point is 220 − (3 × 37) or 109 gm. For each "step" on the abscissa, an ordinate value is calculated as the cumulative survival for *all* observations with body weight *less than* or *equal to* (≤) the "step weight."

For example, the 1st step is 109 gm. Since our data do not contain any animals with weight ≤ 109 gm, we move to the next step (109 + 3 = 112 gm). Our data contain 2 animals (112/d and 110/d) with weights ≤112 gm. Since neither of these animals survived, the cumulative survival (ordinate value) is 0 percent. The next step (112 + 3 ≙ 115) contains 4 animals (112/d, 115/d, 110/d, 114/s) with weights ≤115 gm. The cumulative survival is 25 percent. The cumulative survival is calculated for each of the remaining steps in a similar fashion and is plotted on the ordinate in figure 1. The last step (217 + 3 = 220) includes all animals, and thus has the ordinate value which is the survival (52.6 percent) for all observations.

How does one interpret this cumulative distribution curve to investigate the possibility of a relationship between survival and body weight? Perhaps an insight for this interpretation can be gained from examination of theoretic data. I have generated a sequence of 38 theoretic observations of survival and death by using a table of random numbers to assign 1 observation to each 3-gm step over the range 109 to 220 gm.

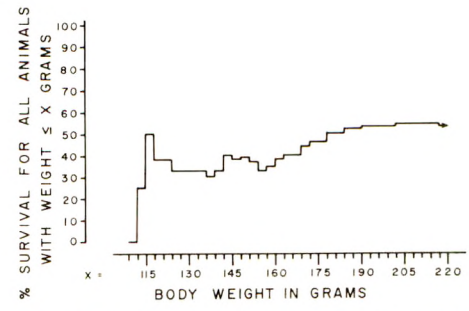


FIG 1. Cumulative distribution curve for survival of 38 rats during the 24-hour period following hemorrhage. (Data from D. L. Wiegman)

Each observation has a 50 percent chance of being a death or a survival and there is no relationship between survival probability and "weight."

A cumulative distribution curve for this theoretic data is shown (fig 2); this curve demonstrates the characteristic of "convergence," in that the percent survival for the first 10 to 16 steps is above *or* below the "real" probability of 50 percent; however, the "error" between the calculated value and the "real" value becomes smaller as more steps are added.

This property of convergence is better demonstrated in another manner. A cumulative distribution curve is arbitrarily constructed for the lower *one-half* (19) of the total number of theoretic observations. This curve appears in the left half of figure 3 for steps from 109 to 163 gm. Another cumulative distribution curve is constructed for the upper one-half (19) of the total number of observations by *starting with the highest* weight and stepping downward (right half of fig 3). In this curve, the ordinate value for each step is the cumulative survival for

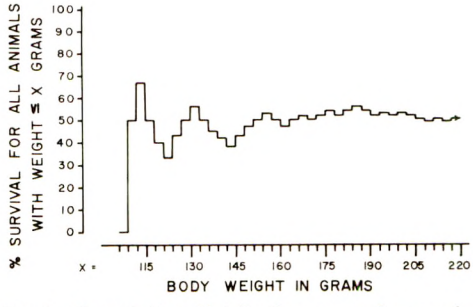


FIG 2. Cumulative distribution curve for survival of 38 "theoretic" animals for which the probability of survival is 50 percent and is independent of body weight. The sequence of survival and death observations was obtained from a random number table.[2]

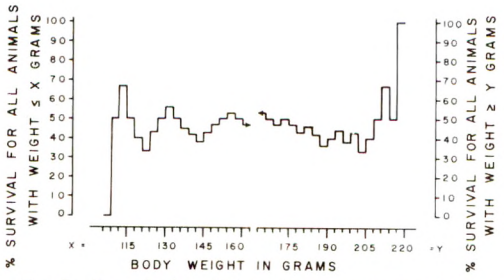


FIG 3. Cumulative distribution curves for survival of 19 "theoretic" animals with weights ≤163 gm (left panel) and 19 "theoretic" animals with weights ≥163 gm (right panel). The sequence of theoretic survival and death observations is the same as used for the cumulative distribution curve in fig 2.

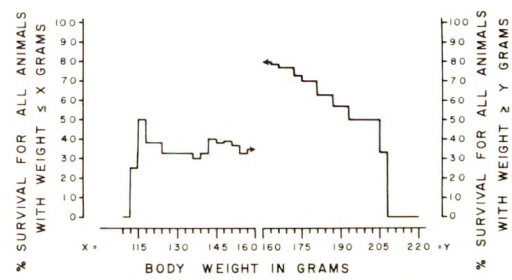


FIG 4. Cumulative distribution curves for survival of 23 rats with weights ≤160 gm (left panel) and for 15 rats with weights ≥160 gm (right panel) during the 24-hour period following hemorrhage. These were obtained from the same raw data as used for the cumulative distribution curve in fig 1.

all observations (theoretic animals) with weight *greater than* or *equal* to (≥) the abscissa value. (For example, the first step is 220 − 3 = 217 and the ordinate is percent survival for all "animals" with weight ≥217 gm.) Figure 3 demonstrates convergence because the survival (47.3%) in the last step (160-163 gm) for the lower cumulative curve (left panel) approaches the survival (52.6% in the last step (166-163 gm) for the upper cumulative curve (right panel). These survivals (47.3% and 52.6%) also approach (ie, converge toward) the "real value" of 50 percent.

Comparison of our animal data (fig 1) to our theoretic data (fig 2) suggests the absence of convergence in the animal data (fig 1). The cumulative distribution in figure 1 appears to converge toward 35 percent until step 163 is reached. Following this step, the cumulative curve appears to converge toward the survival of 52.6 percent for the "last step" (217-220). This suspicion of *divergence* (lack of convergence) is better investigated by arbitrarily dividing the data at the point which precedes the suspected change (step 160).

Figure 4 shows the cumulative distribution curve for 23 animals with weight ≤160 gm (left panel) and that for 15 animals with weight ≥160 gm (right panel). In contrast to "convergence" for our theoretic data in figure 3, our animal data in figure 4 appear to *diverge* (35% survival for the 157-160 step in the left curve and 80% survival for the 163-160 step in the right curve). This suggests that body weight in the 110 to 220 gm range influences survival of hemorrhage. In other words, we would *not predict* that a future rat would have a 52.6 percent probability of being alive 24 hours after hemorrhage, with my colleague's protocol.

As a conclusion to this discussion on probability and cumulative distribution curves, several points need emphasis:

(a) The end (last) step in a cumulative distribution gives a "best estimate" of probability; yet, it does not necessarily give the exact probability (or chance) that an event will happen.

(b) The "lower" and "upper" cumulative distributions can *indicate* convergence if the end step probabilities are as close to each other as in figure 3, or divergence if they are as far from each other as in figure 4. (How close is "close?" This is most appropriately answered by *statistical* tests, which have not been discussed here.)

(c) Cumulative distribution curves usually work very well for 18 or more observations, whereas histograms usually require 40 or more observations to give useful interpretations.

(d) Cumulative distribution curves *do not prove* or statistically test anything; yet, they can lead to a hypothesis which could otherwise be overlooked and which can subsequently be tested statistically.

REFERENCES

1. Harris PD: Statistical Pearls. II. How often did that happen? Anesth Analg 55:357-359, 1976

2. Dixon WJ, Massey FJ: Introduction to Statistical Analysis. New York, McGraw-Hill, 1957

Cerebrospinal Fluid Pressure During O_2 Encephalography and N_2O Inhalation

WILLIAM L. PAUL, MD*
EDWIN S. MUNSON, MD†
JACK E. MANISCALCO, MD‡
Gainesville, Florida§

Cerebrospinal fluid (CSF) pressure was studied in 8 patients and 5 dogs during pneumoencephalography (PEG) or ventriculography in which either O_2 or N_2O was used as the contrast gas prior to and during N_2O inhalation. In 7 patients, the use of O_2 as the contrast gas increased CSF pressure 8.7 torr (range 4 to 12 torr) following N_2O inhalation. In 1 patient, when N_2O was used as the contrast gas, CSF pressure did not change after N_2O inhalation. These findings were confirmed in anesthetized animals ventilated at a constant $Paco_2$. The authors conclude that if N_2O inhalation is required during PEG, maximum patient safety can be achieved if the contrast gas is also N_2O.

THE inhalation of N_2O during pneumoencephalography (PEG) has been shown by Saidman and Eger[1] to markedly increase cerebrospinal fluid (CSF) pressure. Increase in pressure during PEG is related to the differential solubility of N_2O and N_2 in blood, which results in a greater transfer of N_2O from blood to gas than of N_2 from gas to blood. Since N_2O inhalation is commonly used during and after this procedure, some clinicians use O_2 as the contrast gas medium to avoid this hazard.

Although O_2 is more soluble than N_2O in blood, the differential solubility between O_2 and N_2O is sufficiently great that the inhalation of N_2O during O_2 PEG theoretically would increase CSF pressure. Therefore, we measured CSF pressure in patients during PEG, in which O_2 was used as the contrast gas before N_2O inhalation. Anesthetized dogs ventilated at constant levels of $Paco_2$ were similarly studied.

METHODS

Clinical Studies.—Eight patients ranging in age from 10 to 53 years and scheduled for PEG or ventriculography were studied.* Each patient was premedicated with sedative doses of barbiturate and narcotic drugs. Additional sedation was obtained by administering Innovar® IV as necessary. Arterial blood pressure was measured by standard auscultatory methods, and heart and respiratory rates were recorded continuously. Each

*Procedures were performed in accordance with the University's Committee for the Protection of Human Subjects.

*Resident in Anesthesiology.

†Professor of Anesthesiology.

‡Assistant Professor of Neurological Surgery.

§Departments of Anesthesiology and Neurosurgery, University of Florida College of Medicine, J. Hillis Miller Health Center, Gainesville, Florida 32610.

Read at the 50th Congress of the International Anesthesia Research Society, March 14-18, 1976, Phoenix, Arizona.

This study was supported in part by USPHS Grant #GM00427-15.

Paper received: 3/22/76
Accepted for publication: 5/12/76

patient was in the sitting position when studied, and a spinal or ventricular catheter was attached to a pressure transducer. Lumbar subarachnoid or CSF pressure was continuously recorded on a Grass polygraph. Contrast gas in 7 patients was O_2 and in 1 patient was N_2O. All inhaled gases were given at an inflow rate of 10 L/min by face mask attached to a Bain circuit.

Following administration of the O_2 contrast and stabilization of CSF pressure, we recorded control pressures after patient inhalation of 100 percent O_2 for 5 minutes. Patients then inhaled 50 percent N_2O until no further rise in CSF pressure was noted, then N_2O was discontinued and O_2 inspired until CSF pressures returned to control levels. This sequence was repeated 1 to 6 times in each patient, with all patients in the sitting position. The patient given N_2O for contrast also inhaled N_2O 5 times in concentrations ranging from 30 to 70 percent.

Animal Studies.—Additional experiments were performed on 5 male mongrel dogs ranging in weight from 16 to 18 kg. Each animal was anesthetized with pentobarbital (25 mg/kg) and immobilized with pancuronium. Following endotracheal intubation, animals were placed supine and ventilated with O_2, using a volume-limited ventilator. End-tidal CO_2 concentration was continuously monitored with a Godart capnograph to maintain $Paco_2$ values constant within a range of 35 to 45 torr. Blood pressure was recorded by a pressure transducer from a catheter placed in the femoral artery.

With the animal's head in flexion, an 18-gauge spinal needle was placed percutaneously into the cisterna magna and was attached to a pressure transducer to continuously measure CSF pressure. Dogs were ventilated with 100 percent O_2 to obtain control pressures, after which N_2O (50 or 70%) was inspired for 10 minutes. Fluid-gas interchange was achieved by removing 5 to 10 ml of CSF in 1 to 2 ml increments in exchange for equivalent volumes of either N_2O or O_2. When the cisternal administration was complete and CSF pressure had stabilized, N_2O was inhaled in 50 or 70 percent concentrations until no further rise in CSF pressure occurred. When more than 1 gas was studied during the same experiment, N_2O was inhaled before the next contrast gas was administered. If no pressure rise occurred, we assumed that the previous contrast gas had been absorbed.

TABLE 1

Mean ± SD (and Ranges) CSF Pressures During O_2 Encephalography in 8 Patients Following Inhalation of 50% N_2O

Patient number	Age (years)	Contrast volume (ml)	Number of exposures to N_2O	Increase in CSF pressure (torr)
1	48	60	3	11.3 (8-14)
2	20	70	4	8.7 (6-12)
3	53	43	3	6.0 (4-10)
4	28	>20	2	9.5 (7-12)
5	10	>20	1	10.0 –
6*	31	>20	1	7.0 –
7*	32	40	6	8.3 (4-12)
8	19	60	1	22.0† –
Mean	30.4			8.7‡
± SD	15.7			1.9

*Represents ventriculography.

†Value from a patient with hydrocephalus not included in calculations.

‡$p<0.01$.

RESULTS

Clinical Studies.—CSF pressure increased 8.7 torr (range 4 to 12 torr) in 6 patients whose initial CSF pressures were normal (table 1). This increase occurred within 3 minutes (range 2 to 3.5 min). The CSF pressure in 1 patient with known hydrocephalus (initial CSF pressure 20 torr) increased 22 torr. The volume of O_2 injected as a contrast gas ranged from 10 to 70 ml. No correlation between the volume of injected gas and the CSF pressure increase was observed.

No change in CSF pressure was seen in the patient who received N_2O inhalation prior to injection of intrathecal N_2O. No changes in arterial blood pressure or respiratory rate occurred during N_2O inhalation. Both O_2 and N_2O contrast produced satisfactory x-rays.

Animal Studies.—In each animal there was a small increase in CSF pressure (1 to 2 torr) prior to cisternal gas injection, and in arterial blood pressure (10 to 20 torr) during N_2O inhalation (table 2). These pressure changes did not return to control levels when N_2O inhalation was discontinued. Following O_2 encephalography, an increase in CSF pressure of 9.7 torr (range 3 to 21 torr) was observed when N_2O was inhaled in 50 or 70 percent concentration. In 3 animals which also received N_2O injections while breathing N_2O in 50 or 70

TABLE 2
Mean ± SD (and Ranges) CSF Pressure Changes in 5 Dogs During O_2 Encephalography Following N_2O Inhalation

Animal	Contrast volume (ml)	Number of exposures to N_2O	F_IN_2O	$Paco_2$ (torr)	Increase in CSF pressure (torr)
1	30	4	0.5	36	6.5 (5-8)
2	15	3	0.5	35	3.0 –
3	5	1	0.7	33	10.0 –
4	5	1	0.7	35	21.0 –
5	5	1	0.7	38	8.0 –
Mean				35	9.7*
± SD				2	6.8

*$p<0.01$.

percent concentration, no changes in CSF pressure were noted.

DISCUSSION

The inhalation of N_2O during air encephalography, first shown to increase CSF pressure by Saidman and Eger,[1] is a phenomenon related to the 34-fold difference in blood/gas partition coefficients between N_2O (0.46) and N_2 (0.013). Therefore, at the same partial pressure, for every molecule of N_2 that moves from the gas space into the blood, 34 molecules of N_2O move from the blood into the gas cavity. When this differential gas exchange occurs in a noncompliant space, such as the cerebroventricular system, an increase in pressure results.[2]

The differential solubility between N_2O and O_2 also is sufficiently great to produce a gas bubble amplification effect. We calculate that the functional partition coefficient for O_2 is approximately 0.08, the difference between the O_2 content that blood *can* hold (about 20 volumes percent) and the amount present in cerebral venous blood (about 12 volumes percent). These assumptions are supported by the work of Philippart,[3] who observed that the O_2 content of ventricular gas during air encephalography with N_2O anesthesia does not fall below 12 volumes percent. In each patient, the use of O_2 as the contrast gas increased CSF pressure following N_2O inhalation. The same response, although to a lesser degree, was observed in dogs ventilated at constant $Paco_2$ levels.

Gordon and Greitz[4] showed that PEG during N_2O anesthesia in normal patients increased CSF pressure. However, this increase always remained within the normal range. They suggested that N_2O contrast would be safer in patients in whom increased intracranial pressure existed. Recent studies by Elwyn and his colleagues[5] support this recommendation.

Our findings show that the use of O_2 contrast during N_2O anesthesia in patients also elevates CSF pressure. While these changes are moderate and probably clinically insignificant in normal patients, caution must be exercised with patients who have abnormal ventricular systems. Such patients frequently have decreased ventricular compliance, so that small changes in intracranial volume greatly increase CSF pressure. Therefore, N_2O diffusion into the O_2 "space" could produce increased ventricular volume and pressure. Our patient with hydrocephalus showed just such a significant increase in CSF pressure.

We conclude that if N_2O inhalation is used during PEG, the use of O_2 as the contrast gas may be associated with some increase in CSF pressure, but increase of CSF pressure from the contrast gas during N_2O inhalation can be prevented if the contrast gas is also N_2O.

REFERENCES

1. Saidman LJ, Eger EI II: Change in cerebrospinal fluid pressure during pneumoencephalography under nitrous oxide anesthesia. Anesthesiology 26: 67-72, 1965

2. Munson ES: Transfer of nitrous oxide into body air cavities. Br J Anaesth 46:202-209, 1974

3. Philippart C: Contrast gas analysis with air myelography and ventriculography during nitrous oxide anaesthesia. Anaesthesist 18:367-370, 1969

4. Gordon E, Greitz T: The effect of nitrous oxide on the cerebrospinal fluid pressure during encephalography. Br J Anaesth 42:2-7, 1970

5. Elwyn RA, Ring WH, Loeser E: N_2O pneumoencephalography: 5-year experience with 475 pediatric patients. Anesth Analg 55:402-408, 1976

6. Saidman LJ: Complications related to anesthetic solubility, Complications of Anesthesia. Edited by LJ Saidman, F Moya. Springfield, Illinois, Charles C Thomas, Publisher, 1970, p 21

Guest Discussion

RICHARD A. ELWYN, MD
Department of Anesthesiology
University of Utah
Primary Children's Medical Center
Salt Lake City, Utah

Thank you for the opportunity to discuss Dr. Paul's paper. We have been interested in the technic of encephalography since

1965, when Eger and Saidman first suggested the hazards of combining N_2O anesthesia and air contrast medium because of increased CSF pressures.[1] In those instances where N_2O was used in the anesthetic, they suggested that N_2O also be used as the contrast gas. This would decrease operative complications and postoperative morbidity.

Dr. Paul has shown that O_2 can be satisfactorily used as a contrast medium in encephalography, but that the CSF pressure will increase to moderate levels when N_2O is inhaled.

Why then, since 1965 when it was first suggested, has N_2O not been used as the contrast medium for encephalography? The only quoted negative opinion is the 1969 paper by Collan and Iivanainen,[2] which attributed a cardiac arrest to the technic and was explained by the rapid elimination of ventricular N_2O with a fall in CSF. An analysis of that paper reveals other possible causes of the cardiovascular collapse.

When Collan and Iivanainen published their paper, they reported 300 successful cases, where the anesthetic gases were injected as the ventricular contrast medium. At Primary Children's Medical Center, we had completed over 240 pneumoencephalograms in children, using 100 percent N_2O as the ventricular contrast medium and using halothane-N_2O-O_2 anesthesia. We continued to use our technic and have now studied a total of 475 encephalograms.[3] There were no instances of subdural hematoma or cardiovascular collapse following the procedure nor were there any other neurologic complications.

The rationale for general anesthesia in pneumoencephalography is a more comfortable and a quiet patient and thus better and quicker radiologic results. If general anesthesia is chosen, then the optimum advantages of the technic of N_2O anesthesia and N_2O contrast medium can be obtained. All things being equal, we can conduct a safer anesthetic course by eliminating rises in CSF pressure and in minimizing the risk of venous embolism. Postoperatively, the rapid elimination of the ventricular contrast N_2O results in less emesis, less headache, a more comfortable patient, and a more rapid hospital discharge, when compared to air as the contrast medium.

As early as 1951, Davidoff[4] recognized that the aim of treatment in decreasing morbidity from gas encephalography should be the rapid elimination of the contrast medium. Most of the ventricular N_2O will be gone within 15 minutes. Ventricular air may remain for a week or more and be responsible for emesis and headache.

Fatalities occur during and following pneumoencephalography because of the underlying disease, brain herniation, and air embolism. Fatal venous gas embolism has occurred with helium, air, and O_2. It is difficult to understand that the report of 1 cardiovascular collapse in the literature forms the basis for condemnation of a useful technic. If smaller amounts of CSF are removed, the fluid will be replaced rapidly. CSF forms at a rate of 0.4 ml/min and is independent of CSF pressure up to 200 mm H_2O pressure. In our study, we routinely injected 2 to 4 times the amount of N_2O compared to CSF removed. CSF pressures taken within minutes of the N_2O injections were normal. This may help explain our lack of neurologic complications.

Dr. Paul has again shown that CSF pressures increase when N_2O anesthesia is used with contrast gas media other than N_2O. The patient with an abnormal ventricular system may react unfavorably to the increased CSF pressure. For the comfort and safety of patients, N_2O contrast medium and N_2O anesthesia should be considered.

REFERENCES

1. Saidman LJ, Eger EI II: Change in cerebrospinal fluid pressure during pneumoencephalography under nitrous oxide anesthesia. Anesthesiology 26: 67-72, 1965

2. Collan R, Iivanainen M: Cardiac arrest caused by rapid elimination of N_2O from cerebral ventricle after encephalography. Can Anaesth Soc J 16:519-524, 1969

3. Elwyn RA, Ring WH, Loeser E: N_2O pneumoencephalography: 5-year experience with 475 pediatric patients. Anesth Analg 55:402-408, 1976

4. Davidoff LM, Dyke CG: The Normal Encephalogram. Philadelphia, Lea & Febiger, 1951, pp 42-48

Uptake and Excretion of 1-Bromo-1,2,2-Trifluorocyclobutane (42M-9) in Man: Comparative Study on Pharmacokinetics and Metabolism of Inhalation Anesthetics

DUNCAN A. HOLADAY, MD*
VERA FISEROVA-BERGEROVA, PhD†
Miami, Florida‡

1-bromo-1,2,2-trifluorocyclobutane (42M-9) has physical properties similar to those of methoxyflurane and has been suggested for use as an anesthetic agent. Its MAC value, predicted from its lipid solubility, is 0.26 percent. No clinically significant changes were observed in cardiovascular or respiratory function or in clinical laboratory tests. Ventricular dysrhythmias were not seen in this study at analgesic concentrations in contrast to those reported at anesthetic concentrations by others. Pulmonary uptake was high and wash-out was slow. The total amount exhaled comprised 60 percent of the dose. Fluorine, equivalent to 11 percent of total uptake, was rapidly excreted in urine as nonvolatile fluorinated metabolites. An additional 9 percent of 42M-9 was degraded to fluoride and excreted in urine. Since an amount of fluoride equivalent to that excreted in the urine tends to be deposited in the skeleton, approximately 29 percent of uptake may possibly be accounted for as metabolites. Based on fluorine recovery, the fate of 11 percent of 42M-9 uptake remains unknown. The kinetics of uptake, metabolism and excretion of 42M-9 did not differ significantly over a fivefold change of inspired concentration. A comparison of the pulmonary clearance of unaltered 42M-9 and the fraction of uptake converted to urinary metabolites or unrecovered with those of other volatile halogenated anesthetics and their physical properties supports the conclusion that 42M-9 is relatively resistant to biotransformation.

REPORTS of hepatotoxicity and nephrotoxicity following the administration of commonly used halogenated anesthetic agents have stimulated the search for safe alternative volatile anesthetics. The toxicity of halogenated anesthetics is related to metabolism;[1-5] therefore, the search for an ideal agent has turned to compounds which would be metabolized little or not at all.

Compound 42M-9 (1-bromo-1,2,2-trifluorocyclobutane)* has been tested in animals and found to be a stable, potent anesthetic agent.[6] The following study was undertaken to establish the susceptibility of 42M-9 to biotransformation in man and to get information about the pharmacokinetics of its uptake and excretion. The effect of inhaled concentration on extent of metabolism was also investigated.

METHOD AND PROCEDURE

Administration of 42M-9.—The subjects were 8 healthy informed male volunteers averaging 22 (± 2.76)† years of age, of normal build [mean body weight 82 (± 12) kg and body height 181 (± 5.4) cm.] None of

*Dewey and Almy Division, W. R. Grace & Company.

†Data in parentheses following means are standard deviations.

*Professor.

†Associate Professor.

‡Department of Anesthesiology, University of Miami School of Medicine, Miami, Florida 33152.

This study was supported in part by USPHS Grant GM-16498, NIH GRSG RR-5363-14 and Dewey and Almy Chemical Division of W. R. Grace & Company.

Paper received: 12/19/75

Accepted for publication: 3/23/76

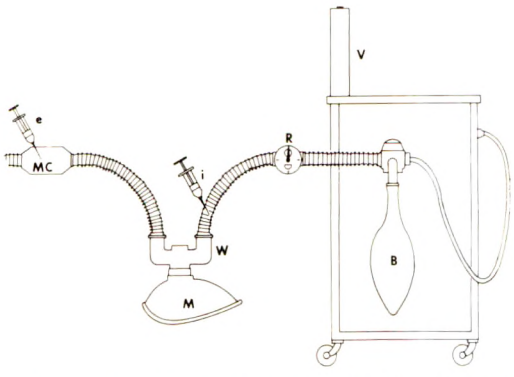


FIG 1. Equipment used for administration of 42M-9 to volunteer. V: vaporizer; B: rebreathing bag; R: Wright respirometer; M: mask; W: 2-way valve; MC: mixing chamber; i: sampling of inhaled air; e: sampling of exhaled air.

the subjects had a history of preexisting disease or drug treatment. 42M-9 was vaporized in a Verni-Trol®* vaporizer and administered in O_2 for 1 hour by mask in a closed, nonrebreathing system (fig 1). Pulse rate and blood pressure were measured at 5-minute intervals. The ECG was monitored continuously and pulmonary ventilation was measured with a Wright respirometer at 5-minute intervals.

The average concentration of inhaled 42M-9 was 0.047 (± 0.006) percent for 5 volunteers in group I and 0.24 (± 0.026) percent for 3 volunteers in group II.

After 1 hour of exposure, each volunteer returned to breathing room air through the nonrebreathing circuit for an additional 45 minutes, during which monitoring was continued. Thereafter, the volunteer resumed normal activities. Strenuous exercise was discouraged for the rest of the week.

Gas Sampling.—During exposure, inhaled and mixed exhaled air samples were collected in gastight glass syringes† at 5 to 10-minute intervals and immediately analyzed for 42M-9 (fig 1). After exposure, samples of mixed exhaled air were collected each 15 minutes during the first 2 hours, then at intervals of approximately 1 hour for 8 hours, then 4 times a day for 2 days, and finally 3 times a day for the rest of the week. The volunteer inhaled through his nose and exhaled through a nylon mouthpiece into an all-glass apparatus (fig 2).

*Ohio Medical Products, Division of Air Reduction Company, Inc.

†Precision Scientific Instruments, Inc.

After washing the apparatus with exhaled air for 3 minutes, 3 to 5 samples were taken during the next 2 minutes in a gas syringe and were analyzed for 42M-9. At the same time, the pulmonary ventilation was measured over a 5-minute period with a Wright respirometer.

Blood Sampling.—Blood was collected for hematologic, hepatic, and renal function profiles (table 1) and for fluoride determination before the experiment and at 24 and 72 hours after exposure. Samples for fluoride determination were heparinized and refrigerated until analyzed. During exposure, arterial blood was drawn from a radial artery anaerobically into a glass syringe for determination of 42M-9 after approximately 30 and 55 minutes of exposure. These samples were analyzed on the day of collection.

Urine Sampling.—All urine was collected as 12-hour samples in polyethylene bottles for 2 days before the experiment and 5 days after exposure. Urine volume, pH, density, concentration of inorganic fluoride, total fluoride, and nonvolatile fluorine were measured. On the 1st day, random samples of freshly voided urine were analyzed for 42M-9.

Analytical Procedures.—42M-9 in air was determined by injection of 0.2 to 1 ml of

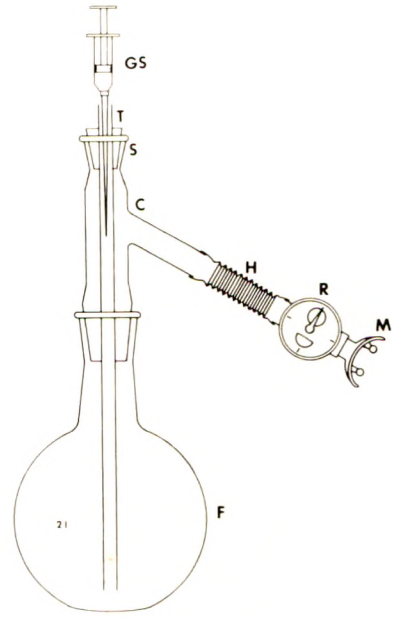


FIG 2. Apparatus for sampling exhaled air. M: mouthpiece; R: Wright respirometer; H: nylon hose; C: glass tube connector; F: glass flask (2-L capacity); S: cork stopper with hole; T: glass tube (ID 6 mm): GS: glass syringe for sampling.

TABLE 1

Clinical Tests in Blood for 42M-9 (Means ± SD)

	Laboratory normal levels	Preexposure	Postexposure	
			24 hours	72 hours
Bilirubin	<1 mg %	0.75 ± 0.49	0.86 ± 0.34	0.74 ± 0.28
Cholesterol	150-250 mg %	198 ± 50	197 ± 37	208 ± 47
Total protein	6.5-8.2%	7.6 ± 0.58	7.8 ± 0.49	7.7 ± 0.51
Albumin	3.5-5.6%	4.7 ± 0.49	4.9 ± 0.52	4.7 ± 0.55
Calcium	9-11 mg %	9.9 ± 0.86	10.2 ± 1.1	9.9 ± 0.55
Phosphorus	3-5 mg %	3.8 ± 1.1	4.1 ± 0.67	4.1 ± 0.47
Alkaline Phosphatase	9-35 IU	17.2 ± 3.5	20.1 ± 3.9*	18.0 ± 3.6
SGOT	8-40 u	23.9 ± 6.6	25.9 ± 9.2	25.0 ± 6.9
Creatinine	0.7-1.5 mg %	1.1 ± 0.19	1.2 ± 0.11	1.2 ± 0.13
Uric acid	2-7 mg %	6.0 ± 1.1	6.3 ± 0.6	6.3 ± 0.9
Urea nitrogen	9-18 mg %	15.3 ± 1.8	16.0 ± 1.8	14.3 ± 1.4
Glucose	70-100 mg %	70 ± 10	79 ± 15	80 ± 17
Hemoglobin		15.5 ± 1.2	15.4 ± 0.7	15.5 ± 1.0
Hct		45.7 ± 3.1	46.5 ± 1.5	47.8 ± 3.9
WBC		6794 ± 1367	7341 ± 1481	8275 ± 1654*
Seg		58 ± 10	54 ± 11	61 ± 7
Lymphs		28 ± 6.3	32 ± 7.0	25 ± 7.6
Monos		7.7 ± 2.4	8.2 ± 3.2	8.6 ± 4.1
Eos		3.9 ± 3.4	4.1 ± 3.8	3.1 ± 1.9

*Significantly higher values, comparing to preexposure levels. $0.01 > p < 0.005$ tested by *t*-test for paired values.

a gas sample into a 2-meter (3 mm ID) glass column packed with 10 percent diisodecylphthalate on Chromosorb P, 60/30 mesh heated to 100° C. A Hewlett-Packard gas chromatograph 7610A equipped with electronic digital integrator 3373B and flame ionization detector was employed for analysis of gas samples. When the concentration of 42M-9 dropped below 0.1 μg/L a Microtek 2500 R equipped with a tritium electron capture detector was employed. Column temperature was 80° C. Standards were prepared by injection of an exactly measured volume of liquid 42M-9 into evacuated glass flasks of known volume. After equilibration to atmospheric pressure an electromagnetic stirrer was used to keep the gas mixture in the jar homogeneous. The magnetic bar was wrapped in aluminum foil in propeller shape to achieve efficient mixing.

42M-9 Concentrations in Blood and in Urine.—After 1 ml of blood was extracted with 1 ml of hexane in a 5-ml glass-stoppered centrifuge tube and shaken gently for 5 minutes, 0.2 to 0.5 μl of extract was injected into a gas chromatograph column connected to an electron capture detector operated as above. Five ml of urine was extracted with 2 ml of hexane in a 10-ml glass-stoppered tube, and the rest of the procedure was the same as for blood. The samples were centrifuged before injection if the phases did not separate spontaneously. Standard curves were constructed by adding 0.2, 0.4, or 0.6 μl of 42M-9, appropriately diluted with hexane to samples of blood and urine obtained before exposure. These samples were analyzed by the same procedure and glassware as for the experimental samples, in order to achieve the same distribution of anesthetic among sample, hexane, and air.

Fluoride in urine[7] *and blood*[8] were determined by direct measurement with a specific fluoride-ion activity electrode. *Nonvolatile fluorine* was measured as fluoride after evaporation of 1 ml of urine at pH 9 on combustion paper in a stream of hot air and combustion in a Schoniger combustion flask.[7]

TABLE 2

Uptake and Pulmonary Desaturation of 42M-9

Volunteer					Administration				Pulmonary desaturation				
									Amount		Half-times‡		
Number	Body weight, kg	Body height, cm	Ventilation, L/min Supine	Ventilation, L/min Normal*	Inhaled air conc, vol %	Relative uptake, %†	Uptake, gm	Blood conc, mg %	gm	% of uptake	VRG, min	MG, min	FG, hr
Group I (0.047%)													
1/I	96	185	7.4	10.4	0.041	34	0.55	2.2	0.48	87	6.3	126	31
2/I	76	182	7.6	10.3	0.047	34	0.50	1.0	0.25	50	5.0	202	16
3/I	79	177	6.2	7.6	0.048	37	0.64	2.0	0.49	77	2.6	144	29
4/I	68	178	6.4	7.5	0.042	60	0.60	1.4	0.42	70	14.5	144	24
5/I	92	180	11.0	9.8	0.057	47	1.40	2.2	0.62	44	1.2	90	31
Mean	82	180	7.7	9.1	0.047	42	0.74	1.8	0.45	66	6	141	26
SD	11.6	3.2	1.9	1.5	0.006	11	0.37	0.54	0.13	18	5	41	6.4
SE	5.2	1.4	0.9	0.6	0.003	5	0.17	0.24	0.06	8	2	18	2.9
Group II (0.24%)													
1/II	64	171	13.5	9.9	0.21	47	4.57	4.5	2.11	48	1.9	78	23
2/II	96	185	7.1	8.6	0.25	46	4.00	8.0	1.90	48	4.8	70	43
3/II	83	188	6.0	9.7	0.26	39	4.30	13.0	2.24	52	5.5	138	20
Mean	81	181	8.9	9.4	0.24	44	4.29	8.5	2.11	49	4	95	29
SD	16.1	9.1	4.1	0.7	0.026	4.4	0.29	4.3	0.19	2.3	2	37	12.9
SE	9.3	5.2	2.3	0.4	0.015	2.5	0.16	2.5	0.11	1.3	1	21	7.2

*Resuming normal activity.

† $\frac{100\ (C_{in} - C_{ex})}{C_{in}}$ at 60th minute of exposure.

‡The half times are derived from the slopes of three exponential functions of the desaturation curve designated as VRG (vessel rich group), MG (muscle group) and FG (fat group).

Total fluorine was determined after combustion of 1 ml of urine sample in an H_2O_2 flame.[8,9] Acidified urine was introduced directly into the flame and the combustion products were trapped in 1N NaOH solution and measured as fluoride ion at pH 6.5.

RESULTS

Hematologic and clinical chemistry measurements are summarized in table 1. The results of all analyses are in the range of normal levels with the exception of 1 volunteer (I/3), who had slightly increased bilirubin (1.2 to 1.4 mg %) and cholesterol (252 to 267 mg %) in preexposure as well as postexposure samples. There were no significant differences between pre- and postexposure values by *t*-test for paired values except for an increase of alkaline phosphatase 24 hours after exposure and an increase of white blood cells on postexposure day 3.

Cardiovascular and Pulmonary Ventilation Data.—Blood pressure remained within normal limits during exposure. No abnormal ECG patterns were observed. Sinus bradycardia (pulse rate <56) occurred during exposure of 3 subjects in group I, representing pulse reductions of 0, 1, and 4 bpm from minimum preexposure rates, and in 1 subject in group II, whose pulse slowed from 60 to 46. Ventilation during exposure averaged 8.2 L/min (± 2.7) and after exposure increased to 9.2 L/min (± 1.2) for both groups (table 2).

Uptake rate, u_t, was determined from the differences between 42M-9 concentrations in inhaled (C_{in}) and mixed exhaled air (C_{ex}) times pulmonary ventilation ($\dot{V}$); the retained dose (D) was determined as the sum of products of uptake rates and time intervals between samplings (t):

$$u_t = \dot{V}\ (C_{in} - C_{ex}) \qquad D = \Sigma u_t t \qquad (I)$$

The relative uptake $\frac{100\ (C_{in} - C_{ex})}{C_{in}}$ at the

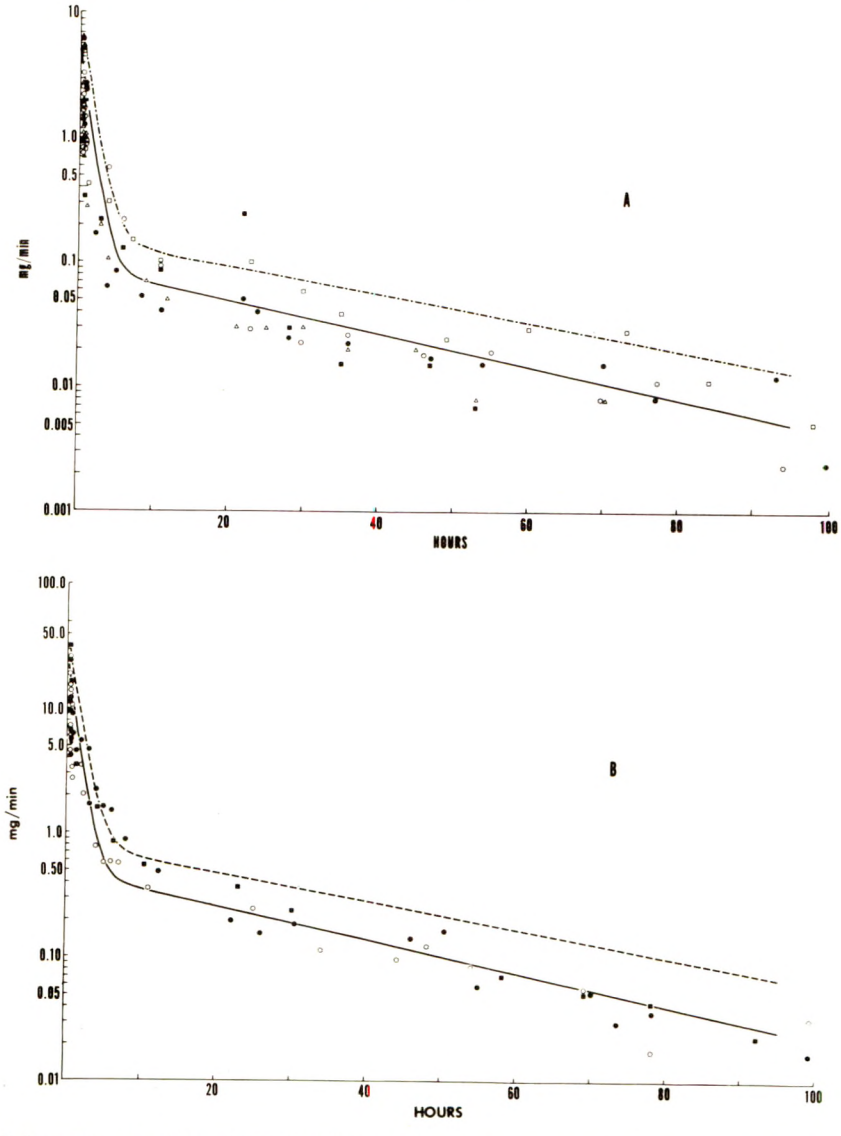


FIG 3. Pulmonary excretion of 42M-9. The excretion rate (mg/min) is plotted against the time after the end of the exposure (hours). Lines are predicted curves: dash lines assume no metabolism (metabolic coefficient equals zero), solid lines account for metabolism (metabolic coefficient = 2.6 L/min). [See text for definition of "metabolic coefficient."] The points represent all measured values in 5 volunteers inhaling for 1 hour 0.047% 42M-9 (A) and in 3 volunteers, inhaling 0.24% (B).

end of 1 hour of exposure approached 43 (± 8.8) percent in both groups (table 2).

42M-9 concentrations in arterial blood averaged 1.8 mg % in group I and 8.5 mg % in group II.

Pulmonary desaturation (table 2) averaged 60 (± 16) percent of the dose. There was no statistical difference between the 2 groups (fig 3).

The parameters of representative desaturation curves described by the sum of 3 exponential functions were determined by searching for optimal fit to the experimental data[7] for each group, using a NONLIN program.* Half-times determined from exponents derived in this manner were 5 minutes, 124 minutes, and 27 hours. There were no significant differences in half-times between the 2 groups (by *t*-test).

A significant increase of *fluoride ion in urine* was observed during the first 5 post-exposure days. In group I, the increase of

*NONLIN is a program for parameter estimation, supplied through the courtesy of Dr. C. M. Metzler of the Upjohn Company.

TABLE 3

Urinary Excretion of Metabolites and Total Recovery of 42M-9

	Fluoride					Organic fluorine					Recovery, % of uptake		
	Urinary excretion					mg* excreted							
Number	mg*	% of uptake	Maximum rate, mg F/12 hr	$t_{1/2}$ hours	Maximum F conc in blood, μg %	Non-volatile	Total	% of uptake	Maximum excretion rate, mg F/12 hr	$t_{1/2}$ hours	In urine	In urine + skeleton†	Total‡
						Group I (0.047%)							
1/I	61	11	3.7	36	10	137	137	24	17	12	36	47	134
2/I	81	16	8.4	10	22	39	—	7.8	12	4	24	40	90
3/I	103	16	6.5	39	19	75	—	12	6	26	28	44	120
4/I	56	9	7.5	16	4	78	—	13	22	7	22	32	102
5/I	42	3	5.7	—	10	57	51	4	9	—	7	10	54
Mean	69	11	6.4	25	13	77		12.2	11	12	23.4	34.6	100
SD	24	5.4	1.8	14	7.3	37		7.5	4.1	10	10.6	14.9	31
SE	11	2.4	0.8	7	3.3	17		3.4	1.8	5	4.7	6.6	14
						Group II (0.24%)							
1/II	181	4	15	25	30	340	332	7	37	22	11	15	64
2/II	288	7	13	21	—	398	—	10	42	18	17	24	72
3/II	235	5	21	24	10	538	538	13	88	25	18	23	76
Mean	235	5.3	16	23	20	425		10	56	22	15.3	20.7	71
SD	54	1.5	4.2	2		102		3	28	3.5	3.8	4.9	6
SE	31	0.9	2.4	1		59		1.7	16	2.0	2.2	2.8	4

*Calculated as 42M-9, 3 fluorine atoms in molecules: mg F $\times \frac{189}{3 \times 19}$.

†The amount of fluoride excretion was doubled because of skeletal uptake of fluoride.

‡Includes pulmonary and renal excretion of 42M-9 and its fluorinated metabolites and skeletal uptake of fluoride.

fluoride was equivalent to 11 percent of administered 42M-9, and in group II, the increase represented 5.3 percent. By *t*-test, this difference is not statistically significant because of large coefficients of variation. Combining the groups, an average of 9 (±5) percent of 42M-9 uptake was excreted as urinary fluoride (table 3). The maximum excretion rate occurred in urine samples collected during the first 12 postexposure hours. The maximum excretion rate in group I was 6.4 mg/12 hr and in group II was 16 mg/12 hr. After the excretion rate reached its peak, the excretion rate in both groups decremented exponentially with a half-time of 24 (± 10) hours.

Organic fluorine in urine in the combined groups was equivalent to 11.4 (± 6) percent of total uptake of 42M-9. It followed closely the excretory pattern of fluoride. The maximum excretion rate occurred in the first 12-hour fraction, and equaled 11 mg/12 hr for group I and 56 mg/12 hr for group II. The half-time of the average excretion curve was 15 (± 8.8) hours. There was no difference between results obtained by the method for nonvolatile fluorine and that for total fluorine.

Fluoride in blood peaked within 2 hours after the end of exposure. The maximum increase of fluoride concentration in blood averaged 13 μg % in the 1st group and 20 μg % in the 2nd group (table 3).

42M-9 in urine was measurable only in urines voided shortly after exposure, and the concentration did not exceed 0.7 mg/L.

DISCUSSION

This study had 3 goals: (1) To determine the uptake, excretion, and biotransformation of 42M-9 in man, (2) to determine the effect

of inhaled concentration on extent of metabolism, (3) to investigate the possibility of utilizing the information from studies of metabolism and pharmacokinetics of new drugs for prediction of biologic effects and their duration. To achieve these goals, all data on uptake and pulmonary and urinary excretion were submitted to mathematical analysis.

The physical properties of 42M-9 are similar to those of methoxyflurane. Its blood/air partition coefficient is 8 and fat/air is 560.[6] As expected, its uptake is great and pulmonary desaturation slow.

The uptake and excretion of unchanged 42M-9 indicate that 42M-9 is metabolized and that the fraction metabolized is independent of inhaled concentration in the range studied, the mathematical analysis of pulmonary desaturation curves indicating that the concentration of 42M-9 in inhaled air affects only the values of intercepts but not the values of the rate constants (fig 3). This is in agreement with a mathematical model of uptake and excretion of inhaled drugs described by 1st order reactions.[10,11]

A differential matrix equation, describing a linear 4-compartmental model,[10] was used for prediction of uptake and desaturation of 42M-9 at a constant inhaled concentration. Considering the lung as the only excretory pathway,[11] the predicted total uptake was lower than the measured total uptake, and the predicted pulmonary desaturation (100%) was greater than the measured desaturation (60%) as demonstrated in table 2. The same observation was made comparing predicted and measured rates of pulmonary desaturation (fig 3, dashed line). The increased uptake and lower desaturation have been attributed previously to metabolic clearance.[10,12] Since only a negligible amount of unchanged 42M-9 was excreted in urine, it is postulated that 40 percent of the dose was metabolized during or following exposure.

The rate of 42M-9 metabolism (mg/min) was estimated from the difference between pulmonary uptake rate at the end of 1 hour of exposure, determined according to equation I, and the calculated retention rate of 42M-9 in tissues of 3 major pharmacokinetic compartments after 1 hour exposure to the measured arterial concentration.[10-12] The mean metabolic rate equaled 9 mg/min in group I and 48 mg/min in group II. The metabolic coefficient (which is the ratio of metabolic rate to inhaled concentration expressed as mg/L),[12] was equal to 2.6 L/min for both groups. The direct dependence of rate of metabolism on inhaled concentration supports the assumption of a 1st order reaction in the range of concentrations studied. This is further supported by the close agreement between the measured rate of pulmonary washout and a desaturation curve predicted by a mathematical model which assumes metabolic clearance to be a 1st order reaction, the rate constant of which is derived from a metabolic coefficient[10] of 2.6 L/min (fig 3).

The fraction excreted as metabolites in urine accounted for 20 percent of uptake and was independent of inhaled concentration, in the range of concentrations used in these studies. The ratio of amounts of 42M-9 exhaled and excreted in urine was the same in groups I (3.34 ± 0.76) and II (3.24 ± 0.51). This supports the conclusion made above from analysis of uptake and pulmonary washout, namely that in the range of concentrations tested, there was no concentration-dependent effect on the extent of metabolism.

Increased fluoride concentration was observed in blood and urine of volunteers exposed to 42M-9. Fluoride concentrations in blood and urine and the pattern of fluoride clearance in group II are comparable to those observed in patients receiving enflurane anesthesia[7] and are smaller than those observed in patients receiving methoxyflurane anesthesia.[8] However, since the concentration of 42M-9 would be twice that used in group II, and as an anesthetic would be used for a longer period, renal impairment similar to that which follows methoxyflurane anesthesia[1,2] might occur.

Increased fluoride was also found in skeletons of mice and rats anesthetized for 2 hours by IP-administered 42M-9. Using a procedure described previously,[13] 1.3 percent of fluorine administered in the form of 42M-9 was recovered from skeletons of mice 48 hours after injection. In similar experiments, 0.6 percent of the dose administered to rats was recovered in skeletons. In these animal studies, the extent of biodegradation to fluoride was not effected by Na-phenobarbital pretreatment.*

The other metabolite, determined in this study as a nonvolatile organic fluorine, was excreted rapidly, and was equivalent to 11 percent of uptake. In terms of latency of

*Fiserova-Bergerova V, Holaday DA: Unpublished data.

TABLE 4
Half-Times of Excretion of Inhalation Anesthetics (Hours)

Drug	Major metabolites			Minor metabolites			Literature reference
	Identity	Time of peak*	$t_{1/2}$	Identity	Time of peak*	$t_{1/2}$	
Isoflurane	F^-	—	—	Organo-fluorine	—	—	16
Fluroxene	CF_3COOH and other nonvolatile fluorine metabolite	24	24	CF_3CH_2OH	11	16	20
Enflurane	Organofluorine	36	88	F^-	7	37	7
Halothane	CF_3COOH Br^-	24 >120	75 300				32-34
42M-9	F^-	<12	24	Organo-fluorine	<12	16	
Trichloro-ethylene	CCl_3CH_2OH	12	24 40	CCl_3COOH $CH_2ClCOOH$	72 1	50, 70† 15	17-19
Methoxyflurane	CH_3OCF_2COOH	22	35	F^- $(COOH)_2$	20 30	48 32	8

*Hours after end of anesthesia when maximum excretion rate occurs.
†Excretion curves exhibit two time constants.

peak excretion and half-time, it is one of the most rapidly excreted metabolites of any anesthetic agent in use (table 4). Another postulated metabolite of 42M-9 is bromide.[6] Our attempt to quantitate its urinary excretion failed because of inadequacy of available analytical methods and because bromide is excreted very slowly and does not follow a regular excretion curve, its excretion being dependent on metabolism and excretion of chloride.[14]

Despite the large availability of 42M-9 for biotransformation, the compound was metabolized to a small extent compared with other soluble anesthetic agents. The major clearance pathways vary for different anesthetic agents, depending on their physical and chemical properties. In general, high vapor pressure and low solubility favor pulmonary excretion; high solubility and chemical instability favor metabolism. The rate of pulmonary clearance of a drug is inversely related to its blood-gas partition coefficient.[15] Accordingly, isoflurane[16] and enflurane[7] are removed from the body mainly by the lung, methoxyflurane[8,9] and trichloroethylene[17-19] by biotransformation. The physical properties of fluroxene favor pulmonary excretion; however, only 60 percent is exhaled.[20]

A number of halogenated anesthetics, arranged in order of increasing blood-gas partition coefficient, are compared in table 5 with respect to fraction of uptake exhaled unaltered and excreted in urine. The high solubility of 42M-9 and its low vapor pressure favor retention; its persistence in the body provides optimum conditions for biotransformation. Since similar fractions of uptake (approximately 60%) of fluroxene[20] and 42M-9 are exhaled despite their different physical properties, it is postulated that 42M-9 molecules are more stable than fluroxene. Similarly, we can postulate that 42M-9 resists biotransformation more than methoxyflurane and trichloroethylene since, despite similar physical properties, a considerably larger fraction of 42M-9 is exhaled than of methoxyflurane[8] and trichloroethylene.[17]

Recovery studies of volatile anesthetics in man have never accounted for 100 percent excretion (table 5). The unrecovered fractions of uptake of the fluorinated volatile anesthetics are related to the quantity of urinary metabolites recovered (table 5) and inversely related to the exhaled fractions. The unexcreted fraction of isoflurane,[16] which is metabolized very little[21] or not at all,[16] is small and could be attributed to experimental errors; but in the cases of enflurane[7] (14%), fluroxene[20] (32%), and methoxyflurane[8] (40%), the unrecovered fraction is so large that another explanation must be given. Other excretory routes, feces[3] and skin,[19,22] were found to be negligible.

It has been shown that as a result of the metabolism of certain drugs[23-31] including

TABLE 5

Excretion of Inhalation Anesthetics

Drug	Blood/gas partition coefficient	Percent of dose excreted: Exhaled unchanged	Major metabolite: Identity	Major metabolite: %	Minor metabolite: Identity	Minor metabolite: %	Unrecovered %
Isoflurane	1.4	95	F^-	0.1*	Organofluorine	0.1	4.8
Fluroxene	1.4	58	CF_3COOH, and other non-volatile fluorine metabolite	10	CF_3CH_2OH	0.6	32
Enflurane	1.9	83	Organofluorine	1.9	F^-	1.0*	14
Halothane	2.4	63	CF_3COOH Br^-	12 12			25
42M-9	8.0	60	F^-	18*	Organofluorine	11.4	11
Trichloro-ethylene	9.5	20	CCl_3CH_2OH	50	CCl_3COOH $CH_2ClCOOH$	19 4	7
Methoxyflurane	12-13	19	CH_3OCF_2COOH	27	F^- $(COOH)_2$	14* 5	40

*The fraction includes urinary excretion and skeletal deposition.

References as in table 4.

halothane,[5,23-25] reactive intermediates are formed which are covalently bound to tissue components. The covalently bound moieties tend not to be excreted, and to be associated with necrosis[5,23-29] and carcinogenicity.[30,31] It is possible that the unrecovered fraction of halothane[32-34] as well as of other anesthetics may also remain covalently bound in the body. A relatively small fraction of 42M-9 remained unrecovered (11%) in our study.

Exposure of volunteers to subeffective and analgesic concentrations of 42M-9 for 1 hour caused *no clinically significant changes in clinical laboratory tests* and cardiovascular parameters. However, Carrow's group[35] reported that anesthetic concentrations of 42M-9 in human subjects resulted in an unusually high incidence of ventricular arrhythmias, which certainly will interfere with its acceptance as a commercial anesthetic agent.

ACKNOWLEDGMENT

The technical assistance of Paul Doleman, BS, Marta Domenech, BS, and Marta Hernandez is gratefully acknowledged.

REFERENCES

1. Taves DR, Fry BW, Freeman RB, et al: Toxicity following methoxyflurane anesthesia. II. Fluoride concentrations in nephrotoxicity. JAMA 214:91-95, 1970

2. Mazze RI, Cousins MJ: Renal toxicity of anaesthetics: with specific reference to the nephrotoxicity of methoxyflurane. Can Anaesth Soc J 20: 64-80, 1973

3. Blake DA, Rozman RS, Cascorbi HF, et al: Anesthesia LXXIV: Biotransformation of fluroxene. I. Metabolism in mice and dogs in vivo. Biochem Pharmacol 16:1237-1248, 1967

4. Harrison GG, Smith JS: Massive lethal hepatic necrosis in rats anesthetized with fluroxene, after microsomal enzyme induction. Anesthesiology 39:619-625, 1973

5. Brown BR Jr, Sipes IG, Carter DE, et al: An animal model of hepatoxicity associated with single-dose halothane anesthesia. American Society of Anesthesiologists Annual Meeting, Abstracts of Scientific Papers, 1975, pp 313-314

6. Dewey and Almy Chemical Division of W. R. Grace & Company: Notice of claimed investigation exemption for a new drug, February 2, 1972

7. Chase RE, Holaday DA, Fiserova-Bergerova V, et al: The biotransformation of Ethrane in man. Anesthesiology 35:262-267, 1971

8. Yoshimura N, Holaday DA, Fiserova-Bergerova V: Metabolism of methoxyflurane in man. Anesthesiology 44:372-379, 1976

9. Holaday DA, Rudofsky S, Treuhaft PS: The metabolic degradation of methoxyflurane in man. Anesthesiology 33:579-593, 1970

10. Fiserova-Bergerova V, Vlach J, Singhal K: Simulation and prediction of uptake, distribution and exhalation of organic solvents. Br J Ind Med 31:45-52, 1974

11. Eger EI II: A mathematical model of uptake and distribution, Uptake and Distribution of Anesthetic Agents. Edited by EM Papper, RJ Kitz.

New York, McGraw-Hill Book Company, Inc, 1963, pp 72-88

12. Teisinger J, Soucek B: Significance of metabolism of toxic gases for their uptake and elimination in man. Cas Lek Cesk 91:1372-1375, 1952

13. Fiserova-Bergerova V: Changes of fluoride content in bone: an index of drug defluorination in vivo. Anesthesiology 38:345-351, 1973

14. Sollmann T: Manual of Pharmacology and Its Application to Therapeutics and Toxicology. Eighth edition. Philadelphia, WB Saunders Company, 1957, pp 1111-1117

15. Severinghaus JW: Role of lung factors, Uptake and Distribution of Anesthetic Agents. Edited by EM Papper, RJ Kitz. New York, McGraw-Hill Book Company, Inc, 1963, pp 59-71

16. Holaday DA, Fiserova-Bergerova V, Latto IP, et al: Resistance of isoflurane to biotransformation. Anesthesiology 43:325-332, 1975

17. Soucek B, Teisinger J, Pavelkova E: The absorption and elimination of trichloroethylene in man. Prac Lek 4:31-41, 1952

18. Soucek B, Vlachova D: Excretion of trichloroethylene metabolites in human urine. Br J Ind Med 17:60-64, 1960

19. Bartonicek V: Metabolism and excretion of trichloroethylene after inhalation by human subjects. Br J Ind Med 19:134-141, 1962

20. Gion H, Yoshimura N, Holaday DA, et al: Biotransformation of fluroxene in man. Anesthesiology 40:553-562, 1974

21. Hitt BA, Mazze RI, Cousins MJ, et al: Metabolism of isoflurane in Fischer 344 rats and man. Anesthesiology 40:62-67, 1974

22. Stoelting RK, Eger EI II: Percutaneous loss of nitrous oxide, cyclopropane, ether and halothane in man. Anesthesiology 30:278-283, 1969

23. Uehleke H, Hellmer KH, Tabarelli-Poplawski S: Metabolic activation of halothane and its covalent binding to linear endoplasmic proteins in vitro. Naunyn Schmiedebergs Arch Pharmacol 279: 39-52, 1974

24. Van Dyke RA, Wood CL: In vitro studies on irreversible binding of halothane metabolite to microsomes. Drug Metab Dispos 3:51-57, 1975

25. Van Dyke RA, Gandolfi AJ: Studies on irreversible binding of radioactivity from (^{14}C) halothane to rat hepatic microsomal lipids and protein. Drug Metab Dispos 2:469-476, 1974

26. Brodie BB, Cho AK, Krishna G, et al: Drug metabolism in man: past, present, and future. Ann NY Acad Sci 179:11-18, 1971

27. Reid WD: Relationship between tissue necrosis and covalent binding of toxic metabolites of halogenated aromatic hydrocarbons, Symposium: Mechanisms of Toxicity by Therapeutic and Environmental Agents. Fifth International Congress on Pharmacology, 1972, pp 194-195

28. Mitchell JR, Jollow DJ, Potter WZ, et al: Acetaminophen-induced hepatic necrosis. I. Role of drug metabolism. J Pharmacol Exp Ther 187:185-194, 1973

29. Plaa GL: Mechanisms of potentiation of CCl_4-induced hepatotoxicity, Symposium: Mechanisms of Toxicity by Therapeutic and Environmental Agents. Fifth International Congress on Pharmacology, 1972, pp 200-201

30. Poirier LA, Weisburger JH: N-hydroxylation and carcinogenesis, Symposium: Mechanisms of Toxicity by Therapeutic and Environmental Agents. Fifth International Congress on Pharmacology, 1972, pp 208-209

31. Magee PN, Hawks A, Stewart BW, et al: Mechanisms of carcinogenesis by alkylnitrosamine and related compounds, Symposium: Mechanisms of Toxicity by Therapeutic and Environmental Agents. Fifth International Congress of Pharmacology, 1972, pp 206-207

32. Cascorbi HF, Blake DA, Helrich M: Differences in the biotransformation of halothane in man. Anesthesiology 32:119-123, 1970

33. Stier A, Alter H, Hessler O, et al: Urinary excretion of bromide in halothane anesthesia. Anesth Analg 43:723-728, 1964

34. Rehder K, Forbes J, Alster H, et al: Halothane biotransformation in man: a quantitative study. Anesthesiology 28:711-715, 1967

35. Carrow DJ, Aldrete JA, Shoemaker DR, et al: Clinical evaluation of a new inhalational anesthetic: 1-bromo-1,2,2-trifluorocyclobutane (42M-9). H Arias, et al, Editor. Recent Progress in Anesthesiology and Resuscitation. Amsterdam, Excerpta Medica, 1975, pp 205-214

Cardiovascular Effects of Lidocaine During Acid-Base Imbalance

RONALD W. YAKAITIS, MD*
JOHN D. THOMAS, MD†
JOHN E. MAHAFFEY, MD‡
Charleston, South Carolina§

Although lidocaine HCl is often given to critically ill patients with ventricular tachyarrhythmias, its use is not without hazard. To investigate whether acid-base disturbances and their subsequent effects on molecular ionization influence cardiovascular (CV) response to lidocaine, dogs in normal acid-base balance, metabolic acidosis, respiratory acidosis, and respiratory alkalosis were given 2 or 4 mg/kg lidocaine IV. Heart rate (HR), PR and QT intervals, MAP, LVEDP, LV dp/dt, and LV dp/dt ÷ CPIP were measured at intervals. In all groups a slight increase in mean HR occurred after 2 mg/kg. Generally, myocardial contractile force was depressed in direct proportion to dose. Essentially, the CV response to lidocaine was not altered by any clinically remarkable degree by pH disturbances. Responses differing from those observed during normal acid-base conditions could not be significantly correlated with changes in pH or $Paco_2$. Results suggest that, in the intact animal, the CV effects of lidocaine, administered in therapeutic doses, are not appreciably influenced by clinically encountered states of acid-base imbalance.

THE antiarrhythmic efficacy of lidocaine hydrochloride has been firmly established.[1,2] Although safe in most instances, overdosage may cause profound hypotension, and clinical conditions that reduce distribution volume or hamper metabolism may cause lidocaine accumulation through delayed plasma clearance.[3]

To some extent, the cardiac action of a local anesthetic may be determined by the degree of drug ionization. Such is the case with procaine, as observed in the isolated heart.[4] Ionization is influenced by the relationship between the dissociation constant (pK_b) and the environmental pH.

As some patients given lidocaine may have significant pH disturbances, these experiments studied, in normal intact dogs, the cardiovascular (CV) response to clinically recommended doses of lidocaine given during commonly-encountered states of acid-base imbalance.

METHODS

Twenty-eight mongrel dogs, 12 to 20 (mean 15) kg in weight, were anesthetized with chloralose (50 mg/kg) and urethane (750 mg/kg). Succinylcholine (2 mg/kg) was administered IM to prevent movement during measurements. After intubation, ventilation with air was controlled with a Bird® Mark 8 respirator. Tidal volume was adjusted to maintain $Paco_2$ at 35 to 45 torr. Left ventricular end-diastolic pressure (LVEDP) was measured with a Statham SF-1 catheter-tip transducer inserted

*Assistant Professor. Present address: Department of Anesthesiology, University of Arizona College of Medicine, Tucson, Arizona 85724.

†Professor.

‡Professor.

§Department of Anesthesiology, Medical University of South Carolina, Charleston, South Carolina 29401.

Paper received: 1/7/76
Accepted for publication: 3/15/76

through a femoral artery into the left ventricle. This catheter signal was also channelled through a Statham resistance-capacitance (RC) differentiator for simultaneous display of left ventricular dp/dt. The remaining femoral artery was cannulated to record aortic blood pressure (BP) through a Statham P23 db pressure transducer. Lead II of the ECG was monitored continuously. All pressure and ECG data were recorded on an Electronics for Medicine DR8 polygraph. Arterial blood-gas determinations were made with a Radiometer ABL-1 analyzer immediately after sampling. Rectal temperature in each dog was maintained, with a heat lamp, at 38 ± 1° C.

Initially, each animal was placed in acid-base balance ($Paco_2$ 35 to 45 torr, pH 7.35 to 7.45, base excess ± 5). Control measurements of heart rate (HR), mean aortic blood pressure (MABP), LVEDP, and the first derivative of left ventricular pressure (LV dp/dt) were made. An additional estimate of myocardial contractility (dp/dt ÷ CPIP)* also was calculated. The PR and QT intervals of the ECG were also measured. Lidocaine (1%) was then injected IV, 14 dogs receiving a dose of 2 mg/kg and 14 receiving 4 mg/kg.

Measurements were repeated 1, 5, and 20 minutes after injection. Thirty minutes after the last measurement, a randomly selected state of metabolic acidosis ($Paco_2$ 35 to 45 torr, pH 7.05 to 7.15, base excess <-5), respiratory acidosis ($Paco_2$ 70 to 85 torr, pH 7.05 to 7.15, base excess ± 5), or respiratory alkalosis ($Paco_2$ 10 to 15 torr, pH 7.60 to 7.75, base excess ± 5) was induced. Metabolic acidosis was produced with an infusion of 0.3 M lactic acid. Respiratory acidosis was induced by ventilation with 10 percent CO_2 in air. Hyperventilation with air was employed to create respiratory alkalosis.

The prescribed acid-base state having been attained, a 10 to 20-minute period was allowed for CV stabilization. Cardiac measurements were then made before and 1, 5, and 20 minutes after giving lidocaine. In a random manner, no more than 2 abnormal acid-base states were studied in any dog, and each dog received the same dose of lidocaine for each experiment. The continuity of an acid-base state was monitored throughout the observation period by frequent blood-gas analyses.

Mean values for HR, MABP, LVEDP, LV dp/dt, and dp/dt ÷ CPIP were calculated. Paired *t*-tests were used to determine significant differences from control within individual groups. Unpaired *t*-tests were employed to compare changes observed in normal dogs with changes during aberrant acid-base conditions.

RESULTS

Seventy-two experiments were performed in the 28 dogs. Control values for pH and $Paco_2$ were similar between respective groups at both dosages studied (table 1). Mean values for all CV variables measured are presented in tables 2 and 3. In most instances, the greatest alterations in MABP, LVEDP, LV dp/dt, and dp/dt ÷ CPIP

*dp/dt ÷ CPIP = the ratio of LV dp/dt to a common peak isovolumic pressure (CPIP). The denominator is the highest isovolumic pressure common to both control contractions and those following pharmacologic intervention. This formula gives an estimate of myocardial contractile force while minimizing the influence of HR, preload, and afterload in the intact heart.[5]

TABLE 1
Control (Pre-Lidocaine) Values for $Paco_2$ and pH (mean ± SE)

	2 mg/kg		4 mg/kg	
	$Paco_2$, torr	pH	$Paco_2$, torr	pH
NOR	37 ± 1.4	7.38 ± 0.01	38 ± 0.8	7.38 ± 0.01
MAC	41 ± 1.9	7.11 ± 0.01	44 ± 1.1	7.09 ± 0.02
RAC	78 ± 2.6	7.14 ± 0.01	73 ± 1.9	7.14 ± 0.01
RAL	12 ± 1.4	7.69 ± 0.02	12 ± 1.1	7.66 ± 0.02

NOR = Normal acid-base balance
MAC = Metabolic acidosis
RAC = Respiratory acidosis
RAL = Respiratory alkalosis

TABLE 2

Mean Values (SE) During Each Acid-Base State for Cardiovascular Variables Measured 1, 5, and 20 Minutes After Administration of 2 mg/kg Lidocaine

Variable	Time	NOR	MAC	RAC	RAL
HR, bpm	0	140 (8)	122 (9)	111 (8)	187 (10)
	1′	144 (8)	124 (8)	122 (7)	178 (10)
	5′	140 (7)	118 (8)	112 (7)	181 (9)
	20′	140 (8)	124 (8)	115 (8)	171 (9)
MABP, torr	0	126 (7)	114 (5)	126 (12)	102 (6)
	1′	124 (7)	118 (6)*†	128 (14)	105 (6)†
	5′	126 (7)	117 (6)*	125 (13)	105 (4)
	20′	124 (8)	120 (8)	126 (14)	102 (4)
LVEDP, torr	0	4.5 (1.3)	7.4 (1.4)	6.8 (1.7)	3.8 (2.3)
	1′	4.1 (1.4)	9.3 (2.0)*	5.9 (1.3)	5.9 (2.7)*
	5′	4.3 (1.2)	8.2 (2.4)	6.3 (0.9)	4.8 (3.3)
	20′	4.4 (1.5)	8.7 (2.2)	6.9 (1.1)	1.3 (1.4)
LV dp/dt, torr/sec	0	4380 (510)	3488 (422)	3393 (582)	4530 (475)
	1′	3799 (402)*	3294 (494)	3471 (485)†	4113 (504)*
	5′	4155 (436)	3323 (580)	3280 (485)	4437 (538)
	20′	3965 (473)	3721 (751)	3341 (462)†	4642 (599)
LV dp/dt ÷ CPIP	0	45.2 (5.0)	38.3 (3.9)	38.1 (6.3)	55.2 (7.0)
	1′	39.6 (3.8)*	36.0 (4.6)	36.7 (6.1)	50.6 (6.9)*
	5′	41.8 (4.3)*	35.7 (3.9)	36.2 (5.6)	54.2 (7.0)
	20′	43.2 (4.4)*	38.9 (4.7)†	39.6 (5.7)†	57.4 (8.0)

*Significantly different ($p<0.05$) from respective control value.

†Signicantly different ($p<0.05$) change from respective control compared with change exhibited by NOR animals at same interval.

TABLE 3

Mean Values (SE) During Each Acid-Base State for Cardiovascular Variables Measured 1, 5, and 20 Minutes After Administration of 4 mg/kg Lidocaine

Variable	Time	NOR	MAC	RAC	RAL
HR, bpm	0	149 (7)	138 (10)	126 (10)	174 (10)
	1′	149 (8)	135 (10)	124 (10)	175 (12)
	5′	139 (7)*	138 (9)†	120 (11)*	170 (12)
	20′	147 (8)	141 (9)	120 (10)*	178 (14)
MABP, torr	0	123 (4)	118 (11)	116 (9)	107 (6)
	1′	121 (4)	117 (11)	102 (7)*†	104 (7)
	5′	122 (4)	121 (11)	109 (8)*	108 (7)
	20′	126 (5)	127 (11)	113 (7)	108 (8)
LVEDP, torr	0	2.3 (0.9)	6.3 (1.2)	7.1 (2.3)	3.5 (1.5)
	1′	3.7 (1.0)*	9.1 (1.6)*	9.5 (2.8)*	4.6 (1.8)*
	5′	2.3 (1.1)	8.2 (1.4)	8.0 (2.6)	4.7 (1.8)
	20′	2.1 (1.5)	7.8 (1.4)	6.1 (3.1)	3.7 (1.8)
LV dp/dt, torr/sec	0	4432 (342)	3824 (579)	3830 (429)	5118 (677)
	1′	3704 (348)*	3247 (443)*	2965 (483)*	4559 (718)*
	5′	4020 (318)*	3608 (422)	3456 (466)	4677 (589)
	20′	4281 (396)	3854 (460)	3699 (586)	5204 (784)
LV dp/dt ÷ CPIP	0	45.9 (4.3)	45.9 (9.8)	46.3 (6.9)	60.5 (11.2)
	1′	37.7 (3.8)*	38.4 (7.5)*	38.5 (5.9)*	53.4 (11.3)*
	5′	41.6 (4.0)	42.5 (7.6)	41.9 (5.2)	53.5 (10.5)
	20′	44.8 (4.5)	44.2 (8.1)	49.1 (8.0)	64.6 (11.6)

*Significantly different ($p<0.05$) from respective control value.

†Significantly different ($p<0.05$) change from respective control compared with change exhibited by NOR animals at same interval.

TABLE 4
Mean PR and QT Intervals (sec) 1, 5, and 20 Minutes After 2 and 4 mg/kg Lidocaine

PR Interval

	2 mg/kg				4 mg/kg			
	0	1′	5′	20′	0	1′	5′	20′
NOR	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09
MAC	0.10	0.11	0.11	0.10	0.10	0.10	0.10	0.11
RAC	0.11	0.11	0.11	0.10	0.10	0.11	0.11	0.10
RAL	0.08	0.09	0.09	0.09	0.10	0.09	0.10	0.10

QT Interval

	2 mg/kg				4 mg/kg			
	0	1′	5′	20′	0	1′	5′	20′
NOR	0.20	0.20	0.20	0.20	0.20	0.21	0.21	0.21
MAC	0.22	0.22	0.21	0.22	0.21	0.22	0.22	0.22
RAC	0.22	0.21	0.21	0.21	0.21	0.22	0.23	0.22
RAL	0.19	0.20	0.19	0.19	0.20	0.20	0.20	0.21

occurred within 4 to 5 minutes after injecting lidocaine. In 5 to 20 minutes, these values generally returned toward control levels. Maximum deviations in heart rate tended to be more dispersed throughout the 20-minute observation period. No group demonstrated appreciable ECG changes of either configuration or intervals (table 4).

Response to 2 mg/kg Lidocaine.—Mean HR within each group did not change significantly. However, dogs in respiratory alkalosis experienced a slight slowing of HR instead of the increased rate exhibited by other groups. Although the mean change in HR at 1 minute was highest (+9.6%) during respiratory acidosis, this change was not significantly greater than that demonstrated by dogs in normal acid-base balance.

Changes in MABP were clinically insignificant.

Values for LV dp/dt and dp/dt ÷ CPIP were generally depressed after lidocaine; a slight increase in LV dp/dt and decrease in LVEDP were noted with respiratory acidosis.

Response to 4 mg/kg Lidocaine.—HR was not remarkably affected at this dose. During respiratory acidosis, the progressive fall in HR and decrease in BP were significantly different from those observed after 2 mg/kg. At 1 minute, both indices of myocardial contractility were appreciably reduced in all animals. The degree of depression in each group was of similar magnitude. In response to decreased contractility, all groups manifested a significantly increased mean LVEDP at 1 minute.

DISCUSSION

Given in the recommended bolus dose of 0.5 to 1.5 mg/kg, the therapeutic plasma concentration of lidocaine is 2 to 5 mcg/ml. This dosage does not appear to significantly depress CV function, even in patients with underlying hypertensive, valvular, or coronary heart disease.[1,6,7] Generally, low doses of lidocaine will actually increase heart rate, systemic arterial pressure, and cardiac output. This phenomenon has been ascribed to a central cardiostimulative effect of the drug.[8]

Administration of lidocaine is not entirely without hazard. Central nervous system signs of drowsiness proceeding to convulsions may be the initial indications of toxicity. These signs may become evident at plasma levels as low as 5 to 6 mcg/ml.[9] Rapid injection or absolute or relative overdosage may cause profound hypotension.[10] Electrophysiologic complications such as sinus standstill and A-V block have occurred, even with approved dosages.[11,12]

Several hypotheses for untoward effects may be proposed. First, a single IV injection of 50 to 100 mg of lidocaine has a pharmacologic half-life of 10 to 20 minutes and

an elimination half-life of 1 to 2 hours. Metabolism to inactive products takes place in the liver. With liver dysfunction and volume distribution abnormalities, a substantial prolongation of the elimination phase was found[3] in patients with hepatic cirrhosis or congestive heart failure. Unless total dosage is reduced in the presence of these disease states, cumulative drug effects will occur much sooner than in normal individuals.

Second, it has been shown that the increased extracellular K^+ concentration which surrounds ischemic or infarcted tissues will enhance the depressant properties of lidocaine.[13] Thus, normally therapeutic blood levels may cause toxic manifestations in a hyperkalemic milieu.

Third, the degree of ionization of the molecules of a local anesthetic partially determines its local and systemic effects. Ionized lidocaine is primarily responsible for conduction block inside the peripheral nerve.[14] Using procaine in an isolated heart preparation, elevation of the stimulation threshold and prolongation of conduction time appear to depend upon the concentration of ionized molecules, while the nonionized drug is responsible for negative inotropic activity.[4]

According to the Henderson-Hasselbalch equation, degree of ionization depends on the relationship between pH and pK_a, the pH at which 50 percent of a given drug is ionized. Since local anesthetics are weak bases (lidocaine $pK_b = 7.86$), an acidotic medium will cause more ionization; an alkaline environment maintains the molecule in its lipid-soluble, nonionized form. At pH values of 6, 7, and 8, the percentages of ionized lidocaine in solution are 98.6, 88, and 42 percent, respectively.

In vitro heart studies with lidocaine, similar to those with procaine, have not been reported; however, at least one toxic effect of lidocaine is influenced by pH: the cortical seizure threshold to lidocaine in intact cats is lowered as $Paco_2$ increases.[15] This finding suggests that a high intraneuronal CO_2 concentration may generate enough intracellular acidosis to significantly increase the concentration of the pharmacologically active lidocaine cation.

Critically ill patients often have associated acid-base derangements. In our study, a clinically representative pH spectrum was induced in intact dogs. Administration of 2 and 4 mg/kg of lidocaine to dogs in acid-base balance produced changes in HR, MABP, and myocardial contractile force similar in magnitude to those observed by other investigators.[16] Deviations in pH within the range of 7.1 to 7.7 did not appreciably alter the effect of lidocaine on the CV variables measured.

Dogs in respiratory acidosis tended to be more susceptible to tachycardia and hypotension, respectively, after 2 and 4 mg/kg of lidocaine. However, this sensitivity could not be significantly correlated with changes in either pH or $Paco_2$. Although independent of pH, myocardial contractile force did appear to decline in proportion to the dose of lidocaine. A notable exception was the slight increase in LV dp/dt and subsequent decrease in LVEDP produced by injecting 2 mg/kg during respiratory acidosis. This heightened inotropy may have been apparent only because it was accompanied by a concurrent increase in HR.

It is possible that compensatory mechanisms in the intact animal were responsible for the inability to demonstrate greatly altered responses to lidocaine in the presence of pH abnormalities. Isolated heart studies would be necessary to delineate the direct effects of lidocaine interaction with pH and CO_2. More intricate electrophysiologic analyses might have revealed subtle effects on conduction. Higher doses of lidocaine at greater extremes of pH might also provide other results. However, such conditions are not relevant within the usual realm of clinical experience.

Whether the antiarrhythmic properties of lidocaine are substantially affected by pH alterations remains to be determined. To the extent that animal data may be applied to man, our results suggest that the response of the normal intact heart to lidocaine, administered in currently recommended doses, is not modified to a clinically significant degree by routinely encountered states of acid-base imbalance.

REFERENCES

1. Gianelly R, von der Groeben JO, Spivack AP, et al: Effect of lidocaine on ventricular arrhythmias in patients with coronary heart disease. N Engl J Med 277:1215-1219, 1967

2. Southworth JL, McKusick VA, Pierce EC, et al: Ventricular fibrillation precipitated by cardiac catheterization. JAMA 143:717-720, 1950

3. Thomson PD, Melmon KL, Richardson JA, et al: Lidocaine pharmacokinetics in advanced heart failure, liver disease, and renal failure in humans. Ann Intern Med 78:499-508, 1973

4. Baird WM, Hardman HR: An analysis of

the effect of pH, procaine cation, nonionized procaine and procaine ethylchloride cation upon cardiac conduction time, stimulation threshold, amplitude of contraction and the relationship of these parameters to antiarrhythmic activity. J Pharmacol Exp Ther 132:382-391, 1961

5. Mason DT: Usefulness and limitations of the rate of rise of intraventricular pressure (dp/dt) in the evaluation of myocardial contractility in man. Am J Cardiol 23:516-527, 1969

6. Grossman JI, Cooper JS, Frieden J: Cardiovascular effects of infusion of lidocaine in patients with heart disease. Am J Cardiol 24:191-197, 1969

7. Schumacher RR, Leiberson AD, Childress RH, et al: Hemodynamic effects of lidocaine in patients with heart disease. Circulation 37:965-972, 1968

8. Kao FF, Jalar UH: The central action of lidocaine and its effect on cardiac output. Br J Pharmacol 14:522-526, 1959

9. Fink BR: Acute and chronic toxicity of local anaesthetics. Can Anaesth Soc J 20:5-16, 1973

10. Austen WG, Moran JM: Cardiac and peripheral vascular effects of lidocaine and procainamide. Am J Cardiol 16:701-707, 1965

11. Cheng TO, Wadhwa D: Sinus standstill following intravenous lidocaine administration. JAMA 23:790-792, 1973

12. Gupta RK, Lichstein E, Chadda KD: Lidocaine-induced heart block in patients with bundle branch block. Am J Cardiol 33:487-492, 1974

13. Singh BN, Vaughan Williams EM: Effects of altering potassium concentration on the action of lidocaine and diphenylhydantoin on rabbit atrial and ventricular muscle. Circ Res 29:286-295, 1971

14. Ritchie JM, Ritchie BR: Local anesthetics: effect of pH on activity. Science 162:1395-1396, 1968

15. de Jong RH, Wagman IH, Prince DA: Effect of carbon dioxide on the cortical seizure threshold to lidocaine. Exp Neurol 17:221-232, 1967

16. Constantino RT, Crockett SE, Vasko JS: Cardiovascular effects of lidocaine. Ann Thorac Surg 8:425-436, 1969

UNEXPLAINED HEPATITIS FOLLOWING HALOTHANE (UHFH). Two hundred and three patients (177 received halothane) developed postoperative jaundice and were evaluated as to etiology by a panel of hepatologists without knowledge of the anesthetic drugs utilized. After excluding all patients with an identifiable cause for the jaundice there remained 76 patients with unexplained hepatitis following halothane (UHFH). Ninety-five percent (71 patients) had been previously exposed to halothane and over half had received the drug within 4 weeks. Of the 76 patients with UHFH 9 had experienced unexplained jaundice after previous halothane exposure and in 7 of these the latent period before the onset of jaundice was shorter during the current episode. Twenty-nine were obese, 52 were aged 41-70 and 53 were female. Twenty patients in the UHFH were subsequently anesthetized without halothane and manifested no hepatic dysfunction although a "halothane free" machine was used in only 1 case. The overall death rate was 23 percent and 20 percent in the UHFH group. The clinical and biochemical features of UHFH were indistinguishable from viral hepatitis. Presence of autoantibodies and esinophilia were increased in patients with UHFH. The authors conclude that reexposure to halothane at short intervals may cause hepatitis but such a complication is rare. *(Walton B, Simpson BR, Strunin L et al: Unexplained hepatitis following halothane. Brit Med J 1:1171-1176, 1976)*

Case History Number 93: Congenital Lobar Emphysema

JOHN T. MARTIN, MD*

IN DECEMBER, 1974, a son was born to healthy parents of an older normal child. The pregnancy, labor, and delivery were medically unremarkable. There was no known family history of congenital anomalies. Within the first month, the diagnosis of Down's syndrome was made, the infant exhibited chronic tachypnea on a routine examination, and his parents reported that his respirations were usually labored or "hard."

At age 8 months, he was hospitalized elsewhere because of "atelectasis" of his right upper lobe (RUL). He recovered after treatment with a chest tube and, perhaps, antibiotics. Neither additional data about his hospitalization nor chest roentgenograms were available from the institution in question.

Because of poor growth and development, the family physician was contacted when the infant was 11 months old. A cardiac murmur was evident at that time, and subsequent cardiac catheterization confirmed the clinical impression of an endocardial cushion defect. Digitalization was begun, for reasons that are uncertain in retrospect.

Evidently the baby was generally healthy until he developed gastroenteritis at age 13 months and was hospitalized with diarrhea, fever, dehydration, and coffee-ground emesis. He was transferred to this Medical Center with the additional diagnosis of pneumonia. He responded to therapy, was subsequently recatheterized to substantiate the diagnosis of endocardial cushion defect, and was maintained on digitalis. The ECG showed a regular sinus rhythm with 1st-degree heart block, right bundle branch block, a left anterior hemi-block, and right ventricular hypertrophy. No comment about chronic respiratory distress was recorded. He was discharged in satisfactory condition.

One month later, at age 14 months, he contracted an upper-respiratory-tract infection. On admission to his home town hospital, congestive heart failure was obvious, and he was transferred to the Medical Center on 30 January, 1976. His weight was 5.2 kg, height 70 cm, rectal temperature 38.3° C, and he had a mild but definite pectus escavatum. The right axillary tube thoracostomy scar was well healed and his liver was enlarged to palpation. Tachycardia, cardiomegaly, and a grade-3/6 pansystolic murmur were evident. Intercostal retraction on inspiration was significant, and medium rales could be heard bilaterally over the lower half of the posterior chest, with coarse, diffuse ronchi throughout all lung fields. His chest x-ray showed bilateral apical infiltrates and right-lower-lobe (RLL) atelectasis. The therapeutic regimen included appropriate antibiotics, furosemide diuresis, postural drainage, chest physiotherapy, 40 percent supplemental O_2 by hood or mask, and continued digitalization.

Respiratory distress continued, with tachypnea (rate 60-80), peripheral cyanosis, progressive atelectasis of the RUL and RLL, and poor aeration of the right hemithorax. Transnasal aspiration of the trachea provoked an ineffective cough and produced minimal amounts of thin, whitish secretions. His conditioned deteriorated slowly. On the 3rd hospital day, because of the onset of respiratory failure with a rate of 110, his trachea was gently and easily intubated transorally with a size-3.5 plastic tube. He received small doses of morphine sulfate IM to permit adequate volumetric ventilation.

To compensate for a poorly fitting endotracheal tube, 100 ml of tidal volume was

*Professor, Department of Anesthesiology, Medical College of Ohio, Toledo, Ohio 43614.

This feature conducted by John T. Martin, MD, Associate Editor.

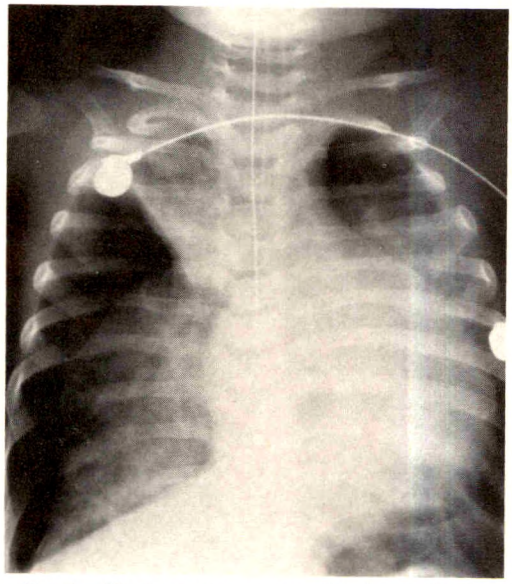


FIG 1. Chest roentgenogram showing collapse of upper and lower lobes. Area lateral to compressed lung tissue showed faint lung markings of hyperinflated RML on original x-ray film.

needed from the respirator. At 35 breaths/min with an F_IO_2 of 0.4, this produced blood-gas values of pHa 7.42, $PaCO_2$ 38 torr, PaO_2 50 torr, SaO_2 88 percent. That evening, the chest x-ray was unchanged, mild respiratory alkalosis was present, borderline hypoxia persisted on the same F_IO_2, a questionable plug of mucus was recovered on tracheobronchial aspiration, his color had improved slightly, and breath sounds were somewhat improved over the right hemithorax. A trial of F_IO_2 0.5 produced little elevation in his PaO_2 (50 up to 54), which his attending pediatric cardiologist attributed to his congenital cardiac defect. An end-expiratory pressure (PEEP) of 3 cm H_2O was added to the ventilatory circuit.

The following morning (hospital day 4) blood-gas values were pHa 7.51, $PaCO_2$ 24 torr, PaO_2 60 torr, on F_IO_2 0.4. Physical examination and chest x-ray were unchanged; the working diagnosis was atelectasis of the RUL and RLL, with an intervening pneumothorax. Review of the chest films by an attending anesthesiologist/intensivist introduced the diagnosis of congenital lobar emphysema with a now-isolated right middle lobe (RML) (fig 1). Bronchoscopy and bronchography followed by lobar resection was suggested. Because of the cardiac anomaly, additional consultations were awaited.

On hospital day 6, the baby was gaining weight, had increasing cyanosis and cardiac failure, urine output was decreasing, and blood from a heel puncture indicated that K^+ and BUN levels were rising. The ECG showed slight digitalis effect but no confirmatory evidence of the alleged hyperkalemia, which was then attributed to the presence of tissue fluid in the blood sample as a result of the heel being squeezed to improve blood flow at the puncture site.

Ketamine-succinylcholine-O_2 anesthesia was administered to permit bronchoscopy and bronchography, which demonstrated an obstructed RML. No foreign body could be found, and the procedure did not improve the RUL and RLL atelectasis. Resection of the RML was agreed upon but was delayed until better control of the baby's fluid and electrolyte status could be achieved. After the bronchoscopy, good diuresis was obtained from furosemide, a mild but compensated respiratory alkalosis was present, and the PaO_2 was acceptable.

Early in the morning of the 7th hospital day, 15 hours after bronchoscopy, the infant began to struggle against the respirator. Since the endotracheal tube was properly positioned, pancuronium in incremental doses up to a total of 0.08 mg/kg was used to restore respiratory control. Tracheal aspirations recovered small amounts of whitish secretions. Good ventilation was evident over the left hemithorax thereafter. Fifteen minutes later, the nurses observed a sudden onset of severe bradycardia, which then became asystole. Resuscitation was begun with 100 percent O_2, delivered by controlled manual ventilation from an anesthesia bag, and closed-chest cardiac compression was started. The heart rate promptly returned to more than 100/min, though the color did not improve. During the resuscitation, the endotracheal tube was briefly displaced into the right mainstem bronchus, was suspected and confirmed by x-ray, and was repositioned into the lower trachea and reconfirmed by x-ray. Following resuscitation, the color remained poor, the pupils were sluggish, the baby was listless without sedation, the hyperkalemia became more intense, and he could be ventilated without requiring pancuronium relaxation.

By midmorning his abdominal girth had begun to increase, unclottable blood was recovered in small amounts when the tracheobronchial tree was aspirated, breath sounds deteriorated over the left lung, and he became mildly hypothermic despite extrinsic

heating. Bradycardia recurred and closed-chest cardiac compression was begun to assist his impaired cardiac output. Shortly thereafter, the heart ceased beating and no effective rate or rhythm could be restored despite all resuscitative drugs, ventilation with 100 percent O_2, and electric shock for 3 episodes of ventricular fibrillation. Necropsy did not define the reason for the obstructed middle lobe bronchus.

DISCUSSION

Hyperinflation of lung tissue as the result of a functioning one-way valve mechanism in the tracheobronchial tree is, fortunately, infrequent. Possible in either the infant or adult, it may present as a respiratory emergency or may unexpectedly complicate the administration of an anesthetic. Awareness of the etiology and pathophysiology of the lesion permits the anesthesiologist to suspect its presence and to modify his management accordingly.

In the adult, hyperinflation of a segment, lobe, lobes, or an entire lung may occur if a functional check-valve develops in an air passage, permitting gas flow on inspiration but obstructing on expiration and trapping gas behind it. The pulmonary tissue distal to the obstruction is gradually pumped up to encroach upon neighboring lung lobes, shift the mediastinum and heart, and, perhaps, to cross the mediastinum and compress portions of the contralateral lung. Symptoms obviously depend upon the amount of hyperinflation and the basic competence of the remaining lung tissue. Whether, and at what point, pulmonary perfusion is impaired is uncertain, but a ventilation/perfusion mismatch can easily be presumed.

At some point, the ability of the check-valve to open on inspiration is undoubtedly terminated by the overexpanded tissue, and the offending portion of the lung becomes bronchially isolated. While controlled ventilation at this point might not further overexpand that portion of the lung, introduction of an anesthetic gas, such as N_2O could easily, were perfusion intact, cause molecular diffusion into the isolated area, thereby increasing its pressure and undoubtedly its volume. Little imagination is needed to understand the undesirable potential of such a process.

Knowledge about congenital lobar emphysema is not new. Meyer[1] reported the entity in 1858, as did Nelson[2] in 1932. Treatment by lobectomy was described by Leahy and Butsch[3] in 1949 and by Robertson and James[4] in 1951. The ball-valve process, which produces hyperinflation as described above, was recognized. However, diagnosis and therapy may be delayed, as in the case presented, if an unwarranted controversy develops over whether the process is primary atelectasis with "compensatory" overexpansion or whether the expansion is primary and collapses adjacent tissue secondarily. Were the former true, one would expect to see a loss of volume in the atelectatic hemithorax with an elevated diaphragm and a mediastinal shift toward the lesion. When, as in the baby presented, the diaphragm of the involved side is flattened and the mediastinum is shifted away from the pathologic process, no case can be made for loss of volume, and the mechanics of the situation becomes clear.

Etiologically, lobar emphysema is not a simple entity. Bronchial obstruction may result from local inflammation, a foreign body, mucosal flaps,[5] softened bronchial cartilages[2,6] which permit bronchial collapse, external compression[7,8] by vessels or tissue masses, anatomically narrowed bronchi,[9] a mucus plug[10] unrecoverable by tracheobronchial aspiration, or a luminal adenoma. No evidence reliably associates congenital lobar emphysema with overvigorous infant resuscitation[10] as has been the case with pulmonary interstitial emphysema.[11,12] Difficulty in demonstrating bronchial obstruction at autopsy permits consideration of the possibility that emphysema has occurred primarily, but this does not account for the clinical picture of overdistension and encroachment. A more detailed etiologic debate is available in Murray's excellent review.[10]

The association of congenital lobar emphysema and heart disease has been well documented.[13,14] In 1 series[14] eight of fourteen cases had heart disease; in another,[13] fourteen of seventeen. Stanger and coworkers[15] demonstrated that either enlarged pulmonary arteries or an enlarged left atrium can compress bronchi. Particularly vulnerable are the left mainstem bronchus and the left upper and right middle lobar bronchi. Associated with this extrinsic bronchial compression is marked softening of the collapsed cartilagenous rings. The two most frequently associated congenital heart lesions are ventricular septal defect (VSD) and patent ductus arteriosus; each produces an increase in pulmonary blood flow.[13] While both the cardiac and the pulmonary lesion may be

severe, hyperinflation is generally the more disruptive situation, and its correction is usually required before cardiac surgery can be contemplated. Pierce's group[13] reported 4 cases of overdistension without adjacent lobe collapse or mediastinal shift, in which they repaired the cardiovascular pathology (2 cases of patent ductus, 1 VSD with pulmonary atresia, 1 Tetralogy of Fallot with absent pulmonary leaflets), with subsequent nonsurgical resolution of the pulmonary the chances of an accidental fluid overload.

Symptomatic congenital lobar emphysema is most frequently treated by surgical excision of the involved lobe(s). Murray[10] reports a mortality rate of 50 percent for nonsurgical "conservative" therapy, with 75 percent of the survivors developing persistent emphysema. Operative mortality in his review was 7 percent. Needle aspiration of the hyperinflated lobe has been tried without acceptable results, or with fatalities.[10] Following lobectomy, most patients enjoy normal growth and development unless hampered by other congenital defects.

Several further problems with the case presented merit comment. Whether the syndrome was present in a mild form shortly after birth is unclear; suspicion that it was is supported by the parents' report of "rapid" and "hard" breathing as a chronic characteristic. Review of the chest roentgenograms from the first admission of this infant to the Medical Center (age 13 months) shows the middle lobe to be hyperinflated and the lower lobe partially collapsed but without flattening of the diaphragm or mediastinal shift (fig 2). The presence of congenital heart disease and pectus excavatum implies vascular compression of the RML bronchus as the etiologic factor in a ball-valve mechanism. It also suggests secondary bronchial chondrodysplasia, and may be a reason for the absence of a pathologic diagnosis of bronchial obstruction at necropsy. Intercurrent respiratory infection undoubtedly was the event that provoked the overt respiratory failure by accentuating underlying pathology in the remaining pulmonary tissue or by obstructing a RML bronchus that was only partially occluded and not previously productive of hyperinflation and encroachment.

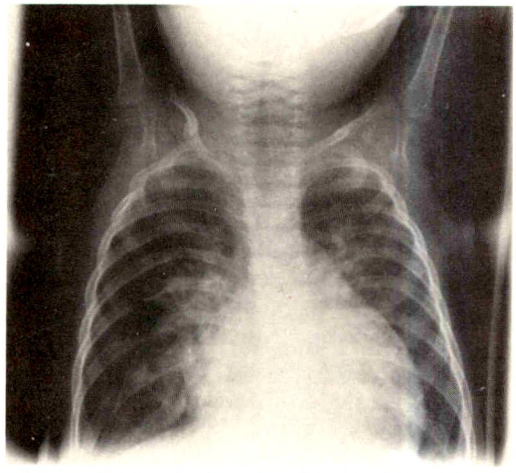


FIG 2. Chest roentgenogram from earlier admission showing partial collapse of RLL with lung markings of encroaching RML visible laterally.

The "pneumothorax" which was treated by a chest tube at age 8 months can be postulated to have been an overdistended RML that was deflated by the chest tube. It is tempting to propose this as a form of decompressive therapy, but literature experience with such an approach has not been encouraging.[10]

Because this infant was intubated and placed on mechanical ventilation without acute worsening of the encroachment, one can presume that the inflammation had fully occluded the RML bronchus by that time. The perfusion status of that lobe is uncertain because hypoxemia can be anticipated from the congenital heart disease and might easily mask shunts attributable to a $\dot{V}/\dot{Q}$ mismatch. Assuming perfusion and shunting to be present, however, one can readily understand why N_2O would be an unwise and rapidly disastrous addition to any anesthetic technic proposed for the infant.

The differential diagnosis of pneumothorax vs congenital lobar emphysema might be difficult under certain circumstances. In this instance RUL and RLL collapse with RML hyperexpansion rendered the right apex and base relatively radiopaque (fig 1), while the intervening area was radiolucent and contained definite but faint lung markings. A pneumothorax usually opacificies the deflated lung, which extends out from the hilum toward a clear periphery, with no lung markings in the radiolucent area, and with a smooth contour for the visceral pleura of the collapsed whole lung. Hyperexpansion of lobes of the left lung may be harder to differentiate from a pneumothorax, but the presence of lung markings in the radiolucent area should cause strong diagnostic suspicion. Should radiolucency extend from the hyperinflated side across the mediastinum without evidence of pneumomediastinum or

subcutaneous emphysema, little danger exists of confusing lobar emphysema with pneumothorax.

Reliance upon blood samples derived from stab wounds in the heel for blood-gas and electrolyte data is not infrequent in pediatric ICU practice. If the heel is not warmed to arteriolize, as nearly as possible, the capillary blood before the stab wound is made, or if it must be squeezed to obtain enough blood for the specimen and tissue fluid is inadvertently obtained, the values obtained may be confusing or misleading. In situations as tricky as in this infant, it would seem that a strong case can be made for an arterial indwelling sampling port to permit accurate measurements with little trauma to the patient. Great concern should be directed toward knowing the exact volume of crystalloids infused into that arterial line, however, and use of a constant-volume pump for this purpose will lessen the chances of an accidental fluid overload.

The demise of this infant was not thought to be an hypoxic event but more likely to be due to electrolyte imbalance, diffuse intrapulmonary hemorrhage, and intractable heart failure. Whether thoracotomy could have been successful immediately after bronchoscopy and bronchography is impossible to deduce retrospectively. Were a similar situation to arise in the future, however, I doubt that the valid reasoning applied to this infant would delay thoracotomy and lobar resection despite the critical nature of the patient's condition.

Lobar emphysema, then, is an infrequently occuring entity which may pose significant problems for the anesthesiologist. Either a mechanical respirator or manual ventilation during anesthesia may worsen a slightly symptomatic hyperinflated lung segment. Should a patient with a bronchially isolated pulmonary subdivision, as existed in the infant discussed here, be anesthetized with N_2O, the probability exists that diffusion of the gas into the isolated alveoli via intact perfusing vessels would augment the hyperinflation and intensify its acute disruptive pathophysiology. Awareness of these situations and of their mechanics might help avoid otherwise potentially fatal respiratory misadventures.

REFERENCES

1. Meyer, 1858, cited by Schneider P: Die Morphologie der Missbildungen des Menschen und der Tiere. Schwalbe E, Editor. Jena, Verlag Gustav Fischer, Chapter 8, 1912, p 827

2. Nelson RL: Congenital cystic disease of the lung. J Pediatr 1:233-238, 1932

3. Leahy LJ, Butsch WL: Surgical management of respiratory emergencies during the first few weeks of life. Arch Surg 59:466-483, 1949

4. Robertson R, James ES: Congenital lobar emphysema. Pediatr 8:795-804, 1951

5. Royes K: Localized pulmonary hypertropic emphysema. Br Med J 2:659-660, 1938

6. Moore TC: Chondroectrodermal dysplasia (Ellis-Van Creveld Syndrome) with bronchial malformation and neonatal tension lobar emphysema. J Thorac Cardiovasc Surg 46:1-10, 1963

7. Potts WJ, Holinger PH, Rosenblum AH: Anomalous left pulmonary artery causing obstruction to the right main bronchus: report of a case. JAMA 155:1409-1411, 1954

8. Pray LGL: Obstructive emphysema in infancy due to tuberculous mediastinal glands. J Pediatr 25:253-256, 1944

9. Mercer RD, Hawk WA, Darakjian G: Massive lobar emphysema in infants: diagnosis and treatment. Report of three cases. Cleve Clin Q 28:270-282, 1961

10. Murray GF: Congenital lobar emphysema. Surg Gynecol Obstet 124:611-625, 1967

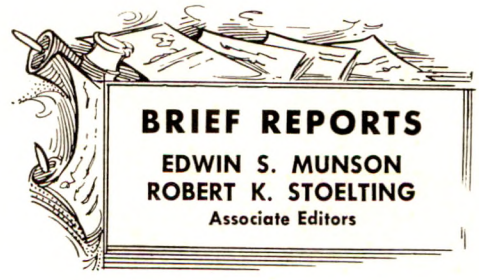
11. Macklin MT, Macklin CC: Malignant interstitial emphysema of the lung and mediastinum as an important occult complication in many respiratory diseases and other conditions; an interpretation of the clinical literature in the light of laboratory experiment. Medicine 23:281-358, 1944

12. Salmon GW, Forbes GB, Davenport H: Air-block in the newborn infant. J Pediatr 30:260-283, 1947

13. Pierce WS, DeParedes CG, Friedman S, et al: Concomitant congenital heart disease and lobar emphysema in infants: incidence, diagnosis and operative management. Ann Surg 172:951-956, 1970

14. Jones JC, Almond CH, Snyder HM, et al: Lobar emphysema and congenital heart disease in infancy. J Thorac Cardiovasc Surg 49:1-10, 1965

15. Stanger P, Lucas RV Jr, Edwards JE: Anatomic factors causing respiratory distress in acyanotic congenital cardiac disease. Pediatr 43:760-769, 1969



Bronchial Blockade in a Child with a Bronchopleural-Cutaneous Fistula Using A Balloon-Tipped Catheter

WILBUR F. CANT, MD*
JOHN H. TINKER, MD
SAIT TARHAN, MD
Rochester, Minnesota§

BRONCHIAL blockade has often been used for airway isolation during thoracic surgery. Whenever infectious processes are combined with the surgical requirement that the diseased hemithorax be positioned uppermost, blockade of the offending bronchus seems desirable. Magill-type blockers, tampons, and other devices previously used are seldom found in operating rooms today. Bronchial blockade in children, involving considerably smaller airways than in adults, has in the past been thought very difficult. It may, in fact, be more important to attempt bronchial blockade in infected pulmonary cases in children than in adults, due to the shorter distances for infectious material to travel to contaminate other pulmonary structures.

The following case is reported to call attention to the ease with which bronchial blockade can be achieved with the Fogarty balloon-tipped arterial embolectomy catheter, and also to illustrate its effectiveness not only in blocking secretions but also in allowing adequate positive-pressure ventilation of the remainder of the lung. Further, the case serves to illustrate that a gastight seal can be achieved with this method.

REPORT OF A CASE

Our patient was a 3-year-old girl weighing 13 kg who was apparently well until approximately 1 year prior to operation, when she developed what was diagnosed as a hemophilus influenza pneumonia. This subsequently became an empyema requiring open drainage. She was discharged with an empyema tube bandaged in place (open to

*Assistant Professor, Department of Anesthesiology.
§Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota 55901.

Paper received: 2/10/76
Accepted for publication: 3/29/76

Classified Advertising (Continued)

ANESTHESIOLOGIST NEEDED—Board Certified desired with supervisory experience, now have three anesthesiologists and thirteen CRNAs doing all types surgery except open heart. Involved in intensive care, respiratory care, pain clinic, school for CRNAs and student and resident training cooperating with Jefferson Medical School. Lovely family community area. Call (412) 539-9711, ext. 273, or send resume to Mr. K. D. Bowman, Assistant Administrator, Latrobe Area Hospital, Latrobe, Pa. 15650. An equal opportunity employer.

CALIFORNIA—ANESTHESIOLOGISTS. Excellent opportunity to practice and participate in academically oriented program. Delightful California city. Favorable plan of remuneration and time off will be worked out. We can pay your professional liability insurance. Send curriculum vitae in first letter to: Jerome S. Harris, M.D., Director of Medical Affairs, Valley Medical Center, 445 S. Cedar, Fresno, California 93702.

ANESTHESIOLOGIST: Board certified/eligible to join newly formed group of anesthesiologists and nurse anesthetists in New Orleans. Fee for service private practice at 650-bed general hospital and newly opened Pediatric hospital. Write or call Metropolitan Anesthesia Associates, 4520 Melpomene, New Orleans, La. 70185. (504) 822-9331.

FACULTY POSITIONS

Department of Anesthesiology, Charity Hospital, New Orleans, affiliated with LSU and Tulane Medical Schools, has three faculty positions open for board certified/eligible anesthesiologists at Associate-Assistant Professor, Instructor levels. Duties involve teaching, research, clinical supervision. Salaries negotiable. Send inquiries and curriculum vitae to: M. Naraghi, M.D., Director, Department of Anesthesiology, Charity Hospital, New Orleans, Louisiana 70140.

MARYLAND: Positions on the Anesthesia Staff at Baltimore City Hospitals. Excellent fringe benefits and salary. Residency fully integrated with the Johns Hopkins Medical School program. Send CV to Peter Chodoff, M.D., Anes-in-Chief, Baltimore City Hospitals, 4940 Eastern Ave., Baltimore, Maryland 21224.

2 American anesthesiologists, eligible for oral boards in April 1977 from world-famous midwestern center, desire to relocate in Ohio or other state if center is attractive. Extensive experience in vascular, neuro and cardiovascular anesthesia. Contact Box 11-76-A in care of I.A.R.S.

ANESTHESIOLOGIST, 38, ABA certified, university trained, excellent references, seeks assoc. partner or group. No geographic preferences, prefer city or suburb. Available June 1977. Write to Box 11-76-B c/o I.A.R.S.

ANESTHESIOLOGIST—LOCUM TENEMS— 1/77 - 3/77 in multispecialty center in NW lower Michigan. Excellent skiing and winter sports area. Michigan licensure necessary. Practice includes cardiac anesthesia and respiratory care. Share call with three other Board certified anesthesiologists. Contact: J. R. Rasmussen, M.D., c/o Burns Clinic Medical Center, P.C., 560 W. Mitchell, Petoskey, Michigan 49770.

ANESTHESIOLOGIST—BOARD CERTIFIED OR ELIGIBLE to assume position as director of and/or consultant to a hospital anesthesiology department in a new, rapidly growing, 171-bed Midwestern hospital; service area covers 150,000 residents and responds to a medical staff of 50-60 physicians; progressive city of 35,000 with excellent schools, cultural activities, and recreational oppotunities; salary $80,000 base and excellent compensation plan. Send c.v. and references to Michael L. Wintory, Director of Personnel, St. Mary's Hospital, 3333 N. Seminary St., Galesburg, IL 61401.

Rates for classified advertising are $3.00 per line, minimum 5 lines. Box number ads $3.50 per line. Classified Display rates on request. Copy deadline 6 weeks prior to publication. Do not submit payment with order; invoices will be sent for payment prior to publication. Ad copy, subject to acceptance by publisher, should be mailed to: Anesthesia and Analgesia . . . Current Researches, 3645 Warrensville Center Rd., Cleveland, Ohio 44122.

CLASSIFIED ADVERTISING

ANESTHESIOLOGY CHAIRMAN

The Hospital Center at Orange has an exceptional opportunity for a Board Certified or Board eligible Anesthesiologist with a minimum of 10 years experience to coordinate the activities of our Department of Anesthesiology as the Department Chairman. An affiliation with Medical School for a student and house officer training program is being pursued. The selected candidate will be considered for academic appointment to the New Jersey College of Medicine and Dentistry.

A competitive compensation package consisting of administrative fee or salary plus fee-for-service income will be available.

The Hospital Center has approximately 400 beds consisting of two units; namely The Orange Memorial Hospital and The New Jersey Orthopaedic Hospital Unit located in suburban N.J. offering convenient access to New York City and Philadelphia.

Send curriculum vitae to:
Arthur T. Dunn, President
THE HOSPITAL CENTER AT ORANGE
188 South Essex Ave.
Orange, New Jersey 07051
Equal Opportunity Employer

CHIEF OF ANESTHESIOLOGY

Major Midwestern medical center with a medical school affiliation is seeking an outstanding Anesthesiologist to head the Department of Anesthesiology. This is an immediate opportunity to restructure and/or build upon our current team. Our compensation package is exceedingly attractive and the working conditions are excellent as a result of our recently completed, multi-million-dollar expansion program. Please send curriculum vitae to: John D. Silbar, M.D., Chairman, Anesthesia Search Committee, Mount Sinai Medical Center, 950 North 12th Street, Milwaukee, Wisconsin 53233.

LOUISIANA—Tulane University, New Orleans. Immediate positions available for Academic Anesthesiologists in new Department of Anesthesiology. Positions in all anesthetic subspecialties, intensive care and respiratory therapy in new university teaching hospital. Tulane University is an Affirmative Action/Equal Opportunty employer. Curriculum vitae to: Robert R. Kirby, M.D., Department of Anesthesiology, Tulane University School of Medicine, 1430 Tulane Ave., New Orleans, Louisiana 70112.

PEDIATRIC ANESTHESIOLOGY RESIDENCY

Childrens Hospital of Los Angeles

Three-phase program: Clinical, Academic, Investigative, emphasizing practical aspects of anesthesiology related to infants and children.

AMA approval for third-year residency. Positions available from two months to one year.

Apply: George B. Lewis, Jr., M.D.
Head, Division of Anesthesiology
Childrens Hospital of Los Angeles
4650 Sunset Boulevard
Los Angeles, California 90054
Phone (213) 660-2450, Ext. 2262

DIRECTOR/SCHOOL OF NURSE ANESTHESIA. Immediate opening for CRNA with Masters Degree. We have a two-year program with university and medical school affiliation leading to a B.S. degree and CRNA certification. Ability to work independently in curriculum formation and school supervision is essential. Excellent salary and benefit package. If you are seeking a challenging position and career in a large medical teaching center, send resume with salary history and requirements to: Mrs. Anna Barker, Employment Manager, Medical Center Hospitals, Norfolk General Hospital Division, 600 Gresham Drive, Norfolk, Virginia 23507.

FACULTY POSITIONS

New University Department of Anesthesiology seeks full-time faculty (all levels) with interests in intensive care, ambulatory and obstetrical anesthesia. Also, full-time director of pediatric (not neonatal) intensive care and respiratory therapy. Challenging positions for those genuinely interested in teaching students and residents, research and development of a new Department. Pleasant university oriented community of 1,000,000. Excellent schools and living areas. Salaries negotiable. Send curriculum vitae to: R. Bryant Roberts, M.D., Professor and Chairman, Department of Anesthesiology, Wright State University School of Medicine, Dayton, Ohio 45431.

CHIEF ANESTHESIOLOGIST for 200-bed hospital—five modern OR's. All surgical services except open heart and neurosurgery. Excellent job challenge. Salary based on past experience and type of appointment. No malpractice insurance required. For information call or write to Dr. Zwemer, Chief Surgeon, Phoenix Indian Medical Center, 4212 North 16th Street, Phoenix, Arizona 85016. (602) 263-1200. The Indian Health Service is a Federal Employer and Federal Civil Service or Public Health Commissioned Corps benefits and requirements apply. Preference is given to qualified Indian or veteran applicants. IHS is an equal opportunity employer.

adherence of part of the cuff to the underlying tube, causing puckering of the rest of the cuff—this is especially true in older tubes and when the cuff is wet; (4) vocal cord paralysis from muscle relaxant administration during intubation, with recovery of normal cord function during extubation.

We believe all the above factors contributed to our problem.

The clinician should be aware that flange formation can occur not only in cuffs with a large residual volume but also in those with low residual volume if tubes are old or worn. Therefore, all cuffed tubes should be examined closely prior to insertion. Selection of a smaller and newer tube would probably have prevented our problem.

ACKNOWLEDGMENT

The authors express their gratitude to Mr. S. Weiss for the photography and to Ms L. Stock for secretarial assistance.

REFERENCE

1. Pavlin EG, Nelson E, Pulliam J: Difficulty in removal of tracheostomy tubes. Anesthesiology 44:69-70, 1976

Humidity Output of the Columbia Pediatric Circle

SIVAM RAMANATHAN, MD*
JACK CHALON, MD†
PETER RAND‡
HERMAN TURNDORF, MD§
New York, New York‖

Rackow and Salanitre[1] have stated that infant circles generate enough moisture (through the neutralization of soda lime by CO_2) to satisfy the humidity requirements of *all* pediatric patients. To verify this assumption, we studied the humidity output of this system on a model patient. Variation in inhalation limb humidity at the Columbia valve,[2] in relation to $\dot{V}CO_2$ and fresh gas inflow, are described and discussed during and after a 2-hour period of stabilization. Recommendations for further humidification, when required, are made.

MATERIALS AND METHODS

A model patient was constructed (fig 1) by attaching a 1 or 2-L anesthetic bag to the patient end of the Columbia valve of a Columbia pediatric system, and flowing CO_2 from a calibrated metered source through the tail end of the bag. A Cascade humidifier** was inserted in the expiratory limb of the circle near the valve. A hygrosensor, connected to a Hydrodynamics Electric Hygrometer Indicator,†† was placed at the valve end of the inspiratory limb. Thermistor probes connected to a Yellow Springs multichannel telethermometer‡‡ were placed: (1) near the hygrosensor in the inspiratory limb, (2) at the outlet of the Cascade, and (3) in ambient air. The thermostat of the humidifier was regulated to maintain outlet temperature at 32° C (the mean temperature measured in the

**Bennett Respiration Products, Inc, Santa Monica, California.

††Hydrodynamics, Inc, Silver Springs, Maryland (model 15-3001).

‡‡Yellow Springs Company, Yellow Springs, Ohio (model 45).

*Assistant Professor of Anesthesiology.

†Associate Professor of Anesthesiology.

‡Research Volunteer, Boston University Student.

§ Professor and Chairman, Department of Anesthesiology.

‖New York University Medical Center, New York, New York 10016.

Paper received: 12/15/75
Accepted for publication: 3/29/76

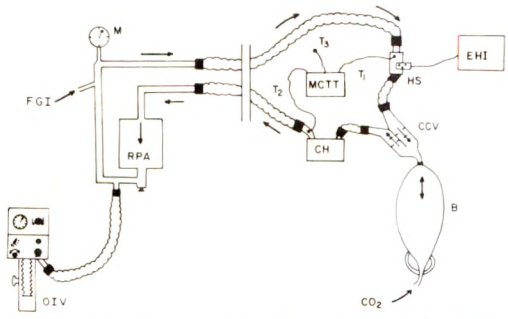


FIG 1. Model patient of Columbia pediatric circle. OIV=Ohio infant ventilator, RPA=Rosewell Park Absorber, FGI=fresh gas inflow from anesthesia machine, M=manometer, EHI=Electric Hygrometer Indicator, HS=hygrosensor, CCV=Columbia circle valve, B=bag receiving CO_2 through its tail end, CH=Cascade humidifier, MCTT=multichannel telethermometer, T1, T2, T3 = thermistor probes: in inspiratory limb, at outlet of Cascade and in ambient air, respectively. A Steen valve on the inspiratory limb is not shown.

endotracheal tube of 10 anesthetized children at the level of the incisor teeth or gums). Ventilation was provided by an Ohio pediatric anesthesia ventilator* (series 300/DO).

Four sets of experiments were conducted using fresh dry systems and CO_2 inputs of 15, 30, 45, and 60 ml/min (3 ml/kg body weight),[3] figures estimated respectively to be the $\dot{V}CO_2$ of children weighing 5, 10, 15 and 20 kg. Ventilator settings, using commonly employed ventilatory parameters, were adjusted as follows: (1) Vt = 50 ml, f = 24; (2) Vt = 100 ml, f = 22; (3) Vt = 150 ml, f = 20; and (4) Vt = 200 ml, f = 18, for the 5, 10, 15, and 20-kg model children, respectively.

All experiments were run with fresh gas inflows (FGI) of 1, 3, and 5 L/min. The canister was filled with 900 gm of soda lime USP. Humidity and temperature measurements were recorded at 15-minute intervals. A 1-L anesthetic bag was used at the patient end of the system for the 5 and 10-kg models and a 2-L bag for the 15 and 20-kg models. Room temperature was recorded throughout the study. All experiments were repeated 5 times. Results represent the mean of 5 individual measurements recorded under identical conditions.

RESULTS

The humidity output of the Columbia pediatric circle *after a 2-hour period of stabilization* ranged from 3 mg/L H_2O with a $\dot{V}CO_2$ of 15 ml/min and an FGI of 5 L/min (fig 2) to 20 mg/L H_2O with a $\dot{V}CO_2$ of 60 ml/min and FGI of 1 L/min. Humidity readings at the onset of all experiments ranged between 2 and 3 mg/L H_2O, reaching approximately 50 to 60 percent of stabilized values within 1 hour. Room air remained at 22 and 24° C throughout all experiments.

DISCUSSION

The humidity output of the Columbia pediatric circle, which ranges from 3 to 20 mg/L H_2O after a 2-hour period of stabilization, is generally within acceptable levels.[4] At an FGI of 1 L/min, all humidity values (fig 2) are above 12 mg/L so long as the $\dot{V}CO_2$ attains or exceeds 30 ml/min. The system should, therefore, be further humidified by vaporizers incorporated into the circuitry when it is used on infants weighing 5 kg or less. The FGI should always be kept around 1 to 3 L/min, as at an FGI of 5 L/min, all humidity values fall short of the minimum recommended level.[4]

Despite these mild disadvantages, the construction of the system is sound. With the exhalation tube placed inside the inhalation tube for a distance of 4 cm, the Columbia valve allows it to act as a heat and moisture exchanger, thus further elevating inspired humidity. The absorber contains a trap which drains out of the system the water formed by the reaction of neutralization, thus preventing encrustation within the apparatus. In addition, all gases exhaled into the system are subjected to the germicidal effect of the lime[5] before reaching the ventilator (or bag), thus reducing respiratory cross-contamination.

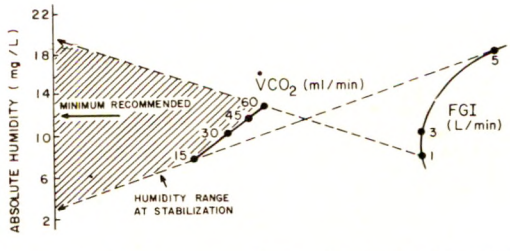


FIG 2. Nomogram predicting the inspired humidity of a child placed on the Columbia circle *after 2* hours of use in relation to $\dot{V}CO_2$ and FGI. Shaded area indicates humidity range of system. To estimate inspired humidity, join FGI value (extreme right) to $\dot{V}CO_2$ (center) and prolong to intersection with humidity line (left.) Read absolute humidity at that point. After 1 hour of use, humidity values are between 50 and 60% of figures derived from this nomogram.

*Ohio Medical Products, Madison, Wisconsin.

REFERENCES

1. Rackow H, Salanitre E: Modern concepts in pediatric anesthesiology. Anesthesiology 30:208-234, 1969

2. Rackow H, Salanitre E: A new pediatric circle valve. Anesthesiology 29:833-834, 1968

3. Smith T: Carbon dioxide: respiratory, circulatory and metabolic effects. 1974 ASA Refresher Course Booklet, Lecture #224, p 2

4. Chalon J, Loew DAY, Malebranche J: Effects of dry anesthetic gases on tracheobronchial ciliated epithelium. Anesthesiology 37:338-343, 1972

5. Wylie WD, Churchill-Davidson HC: A Practice of Anaesthesia. Third edition. London, Lloyd Luke (Medical Books) Ltd, 1972, p 205

Modification of a Bird® Mark-14 Anesthesia Ventilator for Greater Versatility

C. S. JONES, MB, ChB*

THIS anaesthetic machine (figure)† is a Bird® Mark 14 positive-phase ventilator powered via a Bird N_2O-O_2 blender. The selected gas mixture is delivered through a Fluotec® Mark 2 or any other vaporizer of low internal resistance. A ventilation meter is incorporated in the delivery line to monitor ventilating volumes.

When the patient breathes spontaneously, the machine can be set to assist each respiration to the degree judged necessary by the anesthesiologist. The machine can also be programmed to control ventilation.

Adaptation to enable entrainment of the selected gas mix presently involves gas bleed-off from the common line to a reservoir bag. In the primitive form shown, this bleed-off volume is considerably greater than is necessary and a needle valve control could with profit be installed in the bleed-off line to reduce waste.

If the O_2 supply fails, or gas source pressures vary so greatly that the accuracy of the blender is impaired, an audible signal is emitted and the ventilator will not cycle. Under proper working conditions, the blender will not deliver O_2 in less than 25 percent concentration.

†The apparatus described utilizes principles explored and enunciated by Dr. McKesson 65 years ago.

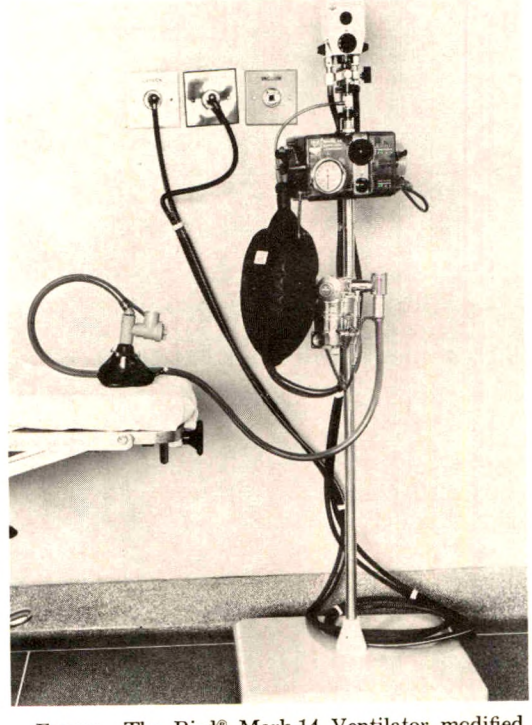


FIGURE. The Bird® Mark-14 Ventilator modified for routine use as a demand-feed anesthetic machine.

This apparatus has been used successfully for over three years, for more than 1000 patients, and for a wide variety of surgical procedures.

*314 Sanlam Building, Worcester, Republic of South Africa.

Paper received: 10/8/75
Accepted for publication: 6/3/76

Decreased Arterial Oxygenation During Sodium Nitoprusside Administration for Intraoperative Hypertension

JOSEPH L. SELTZER, MD*
JOSEPH B. DOTO, JR, MD†
JAY JACOBY, MD, PhD‡
Philadelphia, Pennsylvania§

UNDESIRABLE hypertension is sometimes associated with morphine-N_2O anesthesia for cardiac surgery. Two common approaches to control of such hypertension are the use of chloropromazine[1,2] and the addition of inhalation agents.[3] In the present study, we used sodium nitroprusside to obtain normal blood pressures intraoperatively, finding this procedure generally useful, with one possible hazard.

METHODS

Seven patients who developed hypertension under morphine-N_2O anesthesia for coronary artery surgery were studied. All had received at least 1 mg/kg of morphine sulfate (range 1.06 to 1.6 mg, mean 1.37 mg), d-tubocurarine, and N_2O-O_2 (50:50). Hypertension was considered present when systolic pressure was 50 torr greater than the highest pressure recorded preanesthetically, or was greater than 200 torr. Heart rate, arterial blood pressure, central venous pressure, and arterial blood gases were recorded before and 15 to 30 minutes after the lowering of the blood pressure with 100 μg/ml of sodium nitroprusside in 5 percent dextrose and water.

The drip was started at 20 μg/min and increased until the desired effect was obtained. The mean rate required to control hypertension was 105.7 ± 19.9 μg/min (range 90 to 150 μg/min). The mean total dose at the time of blood-gas drawing was 2.2 ± 0.7 mg (range 1.5 to 3 mg).

TABLE

Mean ± SD (and Range) of Arterial Blood-Gas Tensions and pH Values for 7 Patients Before and After 15 to 30 Minutes of Sodium Nitroprusside Treatment for Intraoperative Hypertension

	Before	After
Pa_{O_2}	219.1 ± 47.9 (134-275)	143.1* ± 34.1 (100-185)
Pa_{CO_2}	33.7 ± 7.7 (21-46)	34.8 ± 7.4 (20-43)
pH	7.42 ± 0.05 (7.36-7.53)	7.44 ± 0.07 (7.38-7.55)

*$p<0.01$.

RESULTS (table)

Mean Pa_{O_2} values decreased 76 torr ($p<0.01$). Pa_{CO_2} and pH did not change significantly. In 4/7 patients, the infusion was required during bypass also. None had any difficulties in terminating the perfusion procedure, and none had any postoperative recall of the procedure.

DISCUSSION

Arens and associates,[1] in 200 patients who received 1.5 to 3 mg/kg of morphine, had 36 patients with hypertension for whom chloropromazine was used after finding droperidol to be ineffective. Conahan's group[2] also reported the use of chloropromazine to treat hypertension associated with morphine anesthesia. Stoelting and coworkers[3] added low concentrations of halothane to 1 mg/kg

*Resident in Anesthesiology, Thomas Jefferson University Hospital. Present address: Division of Anesthesiology, USAF Medical Center, Wright-Patterson AFB, Ohio 45433.

†Clinical Assistant Professor of Anesthesiology.

‡Professor and Chairman, Department of Anesthesiology.

§Thomas Jefferson University, Philadelphia, Pennsylvania 19107.

Paper received: 12/29/75
Accepted for publication: 2/18/76

of morphine and N_2O. Although chloropromazine has been found effective in lowering blood pressure, it is an alpha-adrenergic blocking agent and may cause prolonged hypotensive effects which might hamper termination of bypass. Also, patients may sleep for prolonged periods postoperatively after the large doses necessary to lower blood pressure for a prolonged operation. Halogenated hydrocarbons may also prove undesirable because of their myocardial-depressant effects and their possible potential for visceral toxicity.

Sodium nitroprusside offers a valuable alternative because of its rapid onset and prompt termination of action. Styles and colleagues[4] reported an increase in cardiac output in patients under anesthesia in whom sodium nitroprusside was used to induce hypotension to about 45 torr below control; the blood-gas analysis in their study showed a statistically insignificant decrease in Pao_2. Wildsmith's group[5] reported a marked decrease in Pao_2 in patients given sodium nitroprusside to induce hypotension to a systolic pressure of 50 to 60 torr below halothane-N_2O anesthesia.

The marked fall in Pao_2 in our patients, without changes in pH or $Paco_2$, can be best explained by postulating the opening of intrapulmonary shunts and therefore a change in the ventilation:perfusion ratio. Chatterjee and coworkers[6] demonstrated a decrease in pulmonary vascular resistance and pulmonary artery filling pressures in patients with myocardial infarctions receiving sodium nitroprusside. Another possible explanation would be a fall in cardiac output, which has been reported[7] in unanesthetized hypertensive and normotensive subjects receiving sodium nitroprusside.

REFERENCES

1. Arens JF, Benbow BP, Ochsner JL, et al: Morphine anesthesia for aortocoronary bypass procedures. Anesth Analg 51:901-909, 1972

2. Conahan TJ, Ominsky AJ, Wollman H, et al: Prospective random comparison of halothane and morphine for open heart anesthesia. Anesthesiology 38:528-535, 1973

3. Stoelting RK, Creasser CW, Gibbs PS, et al: Circulatory effects of halothane added to morphine anesthesia in patients with coronary-artery disease. Anesth Analg 53:449-455, 1974

4. Styles M, Coleman AJ, Leary WP: Some hemodynamic effects of sodium nitroprusside. Anesthesiology 38:173-176, 1973

5. Wildsmith JAW, Drummond GB, MacRae WR: Blood-gas changes during induced hypotension with sodium nitroprusside. Br J Anaesth 47:1205-1211, 1975

6. Chatterjee K, Parmley WW, Ganz W, et al: Hemodynamic and metabolic responses to vasodilator therapy in acute myocardial infarction. Circulation 48:1183-1193, 1973

7. Schlant RC, Tsagaris TS, Robertson RJ Jr: Studies on the acute cardiovascular effects of intravenous sodium nitroprusside. Am J Cardiol 9:51-59, 1962

An Anesthetic Gas Scavenger for the Jackson-Rees System

KENNETH J. CESTONE, MD*
WILLIAM P. RYAN, CRNA†
CHARLES D. LOVING, RN‡
Bennington, Vermont§

WE HAVE developed a Plexiglass® gas evacuator‖ (figure) for pediatric systems that vent exhaust gases from the tail of the reservoir bag. It is extremely simple, requiring no additional apparatus, and fits directly into the bag tail, while standard wall-suction tubing fits directly over the outlet at a right angle to the valve. It

‖Manufactured by Anesthesia Associates, Inc, Hudson, New York.

*Staff Anesthesiologist.

†Nurse Anesthetist.

‡Nurse Anesthetist.

§Department of Anesthesiology, Putnam Memorial Hospital, Bennington, Vermont 05201.

Paper received: 2/6/76
Accepted for publication: 3/1/76

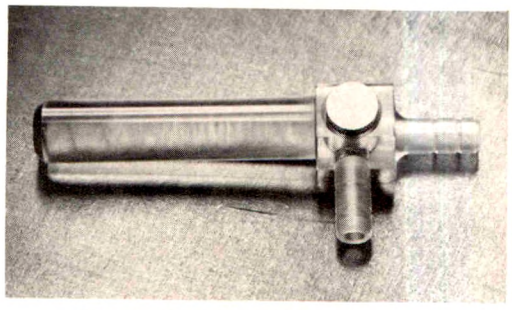


FIGURE. Plexiglass® Gas Evacuator.

incorporates a bag tail overflow valve, enabling the anesthetist to manually control bag distention and inflation pressures at customary gas flows. The unit is most suitable for modified Jackson-Rees systems.

The evacuator is constructed to prevent the suction from either collapsing the bag or affecting gas flow to the patient; only gases exhausted by the pop-off valve are evacuated. With gas flows of 4 to 10 L/min and inflation pressures below 40 torr, no leakage was detected using moderate wall suction.

We have employed the unit clinically and have found it safe, light, effective, and convenient when used as described. It should not be autoclaved, but may be gas or cold-sterilized.

A Method for Inserting the Carden Tube

JAMES E. COOKE, MD*
JUDITH B. HOOD, MD†
JOHN D. THOMAS, MD‡
Charleston, South Carolina§

PREVIOUS investigators[1] have reported difficulty in inserting the Carden tube. Where anatomic abnormality exists, both trainees and attending anesthesiologists often encounter extreme difficulty. We have developed a safe, relatively easy method for inserting the Carden tube when microlaryngoscopy is planned.

We removed 6 cm of the plastic insulation from a 12-gauge copper wire and formed a "U" bend in the wire at the 6 cm point. The wire was then shaped to follow the natural curve of the patients' airway. The exposed copper wire was lubricated and placed in the Carden tube (figure).

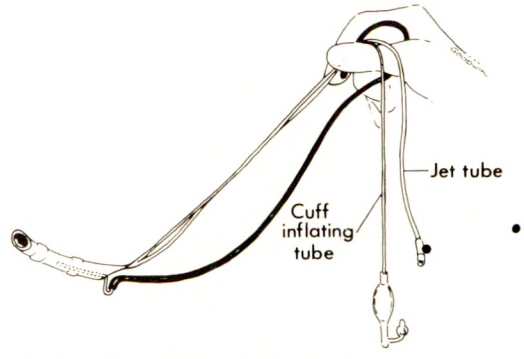


FIGURE. Technic for inserting Carden tube; described in text.

The position of the Carden tube on the stylet is important. The tip end of the stylet should be 1.5 cm from the distal end of the endotracheal tube to prevent injury to the trachea by the stylet. The hump in the stylet is placed at the furthest end of the tube facing posteriorly. This prevents the tube from sliding and turning on the stylet, an additional precaution against injury.

*Assistant Professor of Anesthesiology.
†Chief Resident in Anesthesiology.
‡Professor of Anesthesiology.
§Medical University of South Carolina, Charleston, South Carolina 29401.

Paper received: 2/13/76
Accepted for publication: 3/29/76

During insertion, the cuff tube and jet tube are held between the fingers at the proximal end of the stylet. Under direct vision, the trachea is exposed and the Carden tube inserted to a position with the proximal end just below the vocal cords. The tubes are released, the cuff inflated, and the stylet removed. The cuff is always inflated before removal of the stylet, to avoid accidental dislodgement of the tube.

We have found our insertion technic to be quite simple and to avoid previously-described difficulties. First-year anesthesia residents have found placement of the Carden tube with stylet as easy as insertion of a standard endotracheal tube. We believe use of the stylet is as safe as and more successful than use of Magill forceps or uterine packing forceps.

REFERENCE

1. El-Naggar M, Keh M, Stemmers A, et al: Jet ventilation for microlaryngoscopic procedures: a further simplified technic. Anesth Analg 53:797-804, 1974

Comparison of Dot Test and Digit-Symbol Test for Street Fitness of Outpatients

JOSEPH G. RITTER, MD*
NANCY ANDERSON, MA†

THE Trieger Dot Test has been described[1] as an adequate measure of street fitness for discharge of same-day surgery patients. This test is essentially an adaptation of design 4 of the Bender-Gestalt Visual Motor Test. Since the directions were altered from the original procedure of copying the design and require that the patient connect the dots with a measure of variance used to determine pre- and postoperative scores, previous studies of normal and deviant populations on this test cannot be used to establish the validity and reliability of the test. In addition, scoring of the Trieger is time consuming. Other authors have also suggested criteria for street fitness.[2-5]

As gross motor coordination after anesthesia returns to baseline values more rapidly than fine motor coordination, a measure of fine motor coordination meets one of the criteria essential to establishing the validity of the test. Selection of a widely used and well standardized test would permit the application of already established normative data and reliability studies. Other criteria are that it be short in duration and relatively easy to administer and score. The Digit-Symbol subtest of the WAIS‡[6] and the Coding (Digit-Symbol) subtests of the WISC‡-R[7] and WISC[8] appear to meet these criteria.

METHOD

A 60-day trial was instituted during which both the Trieger Dot Test and the Digit-Symbol Tests were administered to all outpatients for general anesthesia. For the 6-to-8-year age group, the WISC-R Coding Test A (Digit-Symbol); for the 8-to-16-year age group, the WISC Coding B (Digit-Symbol); and for the over-16 group, the WAIS Digit-Symbol subtest were used.

The younger children make 1 or 2 horizontal or vertical lines or a circle inside stars, triangles, etc, in imitation of 5 completed symbols. The adolescent and the adult groups place symbols below prescribed digits duplicating the digit-symbol combinations shown at the top of the test paper. These 2-minute timed subtests provided a measure of speed and accuracy on a routine task yielding a score based on visual discrimination, short-term memory, and fine motor coordination functioning—all basic skills necessary for street fitness. The use

‡WAIS: Wechsler Adult Intelligence Scale; WISC: Wechsler Intelligence Scale for Children.

*Director, North Penn Anesthesia Institute. Anesthesia Department, North Penn Hospital, Lansdale, Pennsylvania 19446.

†Director of Special Education, Montgomery County Intermediate Unit, Blue Bell, Pennsylvania.

Paper received: 8/1/75
Accepted for publication: 2/20/76

of scaled scores rather than raw scores takes advantage of the extensive standardization of both the WISC and the WAIS tests.

The Digit-Symbol Test is administered with the patient seated at a table or in an armchair with a flat surface available and directions are read aloud by the person administering the test. Following a sample practice section, the patient copies the symbols appropriate to the numbers as rapidly as he can during the 2-minute period. The raw score (total number of correct responses) is converted to a scaled score as per the norms established for each age group.[6-8]

After the return to normal of the patient's vital signs and orientation to hospital, doctor, and room number, the same test is administered to the patient under the same conditions. The raw score is converted to a scaled score as per the norms and the result compared with the preoperative scaled score. If the postoperative scaled score is below the preoperative, the patient is retained and the identical test repeated in ½ hour.

Since repeated testing with the same test form with normal subjects results in slightly improved scores, the question of re-test reliability arises. However, in this case the physician is interested in a return of functioning related to street fitness. For improvement in test performance to occur as a result of increased practice, the functions of visual discrimination, short-term memory, and fine motor coordination would have to return to preoperative levels. Thus, repeated testing with the same form can be conducted at ½-hour intervals without interfering with the validity of the measure.

RESULTS

During the period October 1, 1974, to May 30, 1975, 257 outpatients for general anesthesia were tested with the Dot Test. During April and May 1975, 82 outpatients for general anesthesia were given both the Dot Test and the Digit-Symbol Test, according to age. Since June 1, 1975, the Digit-Symbol Tests have been used exclusively on 847 patients.

The subjective evaluation of the staff in the Short Procedure Unit as to ease of testing and ease of scoring was recorded. Variability in the comparative scoring systems for the Dot Test and the Digit-Symbol Test were evaluated, as was the time for arrival in the recovery room until satisfactory scoring was achieved.

In subjective evaluation of ease of administration, the Digit-Symbol Testing required the use of a nurses' aide or ward clerk to administer the test over the 2-minute period prescribed. This time was compensated for, however, by the greater ease of scoring the Digit-Symbol Test. An evaluation of the degree of error is not necessary with the Digit-Symbol Testing as with the Dot Test. In comparing the results of the 2 tests, there were no instances where the Digit-Symbol Test consistently produced a score which mitigated against discharge of the patient, while in ± 10 percent of the cases, the Dot Test consistently produced a worse score postoperatively than preoperatively. Either repeated testing or other situational factors adversely influence the patient's responses with the Dot Test. Nursing personnel chose the Digit-Symbol Test the more time saving and more accurate in evaluating street fitness.

Average time from recovery room to discharge was 286 minutes during the period when the Dot Test was used, 322 minutes when both tests were used, and 175 minutes with the Digit-Symbol test alone.

CONCLUSIONS

Our studies suggest that the Digit-Symbol Tests are easier than the Dot Test to administer, easier to score, provide a better measure of street fitness, and allow for earlier safe discharge of the patient from the ambulatory unit.

REFERENCES

1. Newman MG, Trieger N, Miller JC: Measuring recovery from anesthesia—a simple test. Anesth Analg 48:136-140, 1969

2. Doenicke A, Kugler J, Laub M: Evaluation of recovery and "street fitness" by EEG and psychodiagnostic tests after anaesthesia. Can Anaesth Soc J 14:567-583, 1967

3. Treloar EJ: An outpatient anaesthetic service: standards and organization. Can Anaesth Soc J 14:596-604, 1967

4. Kortilla K, Linnoila M, Ertama P, et al: Recovery and simulated driving after intravenous anesthesia with thiopental, methohexital, propanidid or alphadione. Anesthesiology 43:291-299, 1975

5. Epstein B: Recovery from anesthesia. Anesthesiology 43:285-287, 1975

6. Wechsler D: The WAIS Manual. New York, The Psychological Corporation, 1955

7. Wechsler D: The WISC-R Manual. New York, The Psychological Corporation, 1974

8. Wechsler D: The WISC Manual. New York, The Psychological Corporation, 1949

Acute Maxillary Sinusitis Complicating Nasotracheal Intubation: A Case Report

T. JAMES GALLAGHER, MD*
JOSEPH M. CIVETTA, MD†
Miami, Florida‡

ACUTE maxillary sinusitis is frequently mentioned as one of the complications of nasotracheal intubation. Arens and associates[1] recently reported a 2 percent incidence in a retrospective study. In that group all patients complained of pain or had some other definite symptom, and all responded to antibiotic therapy.

In the acutely ill patient, the diagnosis becomes both more difficult and more important. The patient is usually too ill to complain specifically, and the presence of the tube prevents vocalization. An elevated temperature is of no diagnostic value in a setting of many possible causes. Therefore, in evaluating sepsis, patients with nasotracheal tubes should have sinus films taken as soon as feasible. If the source is not discovered, hematologic seeding[2] and sepsis may occur. The following case exemplifies these problems.

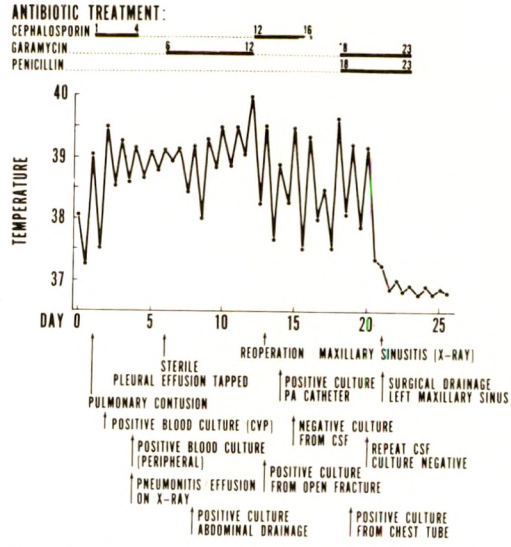


FIG 1. Temperature spikes, with appropriate antibiotics used according to new culture results.

REPORT OF A CASE

A 49-year-old man was hit by a truck, sustaining a pulmonary contusion, partially lacerated pancreas, and an open fracture of the right ulna. Prior to induction of anesthesia for abdominal exploration, an 8.5-mm low-pressure cuff was placed through the nares. No mucosal-shrinking agents were used.

His postoperative course (fig 1) was complicated by respiratory failure, treated by intermittent mandatory ventilation and positive end-expiratory pressure. He became febrile from the time of operation, potential sources including his contused lung, the Swan-Ganz catheter, and the site of his open fracture. Pancreatitis was also considered because of persistent abdominal drainage with high amylase content. Blood cultures grew Streptococcus; Proteus and Herellea were identified in tracheal secretions, and the abdominal drainage contained Enterococcus. Cerebrospinal fluid cultures were negative. As each new positive culture was obtained, sensitivities were checked to insure appropriate antibiotic coverage.

On the 13th postoperative day, abdominal exploration was performed in an attempt to find the source of sepsis. None was discovered, but during the course of anesthesia, a purulent discharge was noted from the right naris. At this time, the nasotracheal tube

*Fellow, Intensive Care Unit, Jackson Memorial Hospital, University of Miami Medical Center.
†Associate Professor of Surgery, Anesthesiology and Medicine, University of Miami Medical School.
‡Departments of Anesthesiology and Surgery, University of Miami School of Medicine, Miami, Florida 33152.
Reprints to Dr. Civetta.
Paper received: 12/2/75
Accepted for publication: 3/2/76

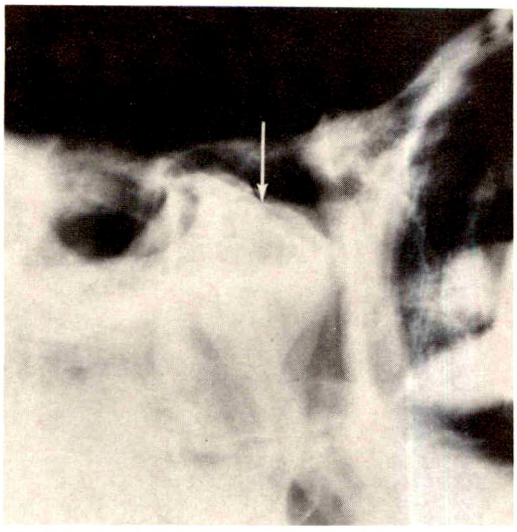


FIG 2. Arrow demonstrates air-fluid level in the maxillary sinus while in the supine position.

was exchanged for an orotracheal tube. This discharge revealed Proteus, Klebsiella, and Citrobacter when cultured.

Postoperatively, the fever continued in spite of appropriate antibiotic therapy. Sinus films were obtained after physiologic stability permitted transport. An air-fluid level was seen in the maxillary sinus (fig 2). There was no evidence on routine films of a maxillary fracture. The sinus cavity was drained shortly thereafter of 30 ml of foul-smelling pus. Proteus, Klebsiella, and Citrobacter were subsequently grown from the cultures. His temperature returned to normal on the following day.

COMMENT

This patient had multisystem failure and the path to the final diagnosis was quite complicated. There is need for a complete and exhaustive search to identify the source of sepsis in the severely ill patient with multiple problems. The case also demonstrates the fallacy of relying on culture reports alone for therapeutic decisions.

The argument that long-term intubation is better tolerated with a nasal tube is not supported by objective data. Since sinusitis as well as other complications[2,3] are more likely to result from nasotracheal intubation, orotracheal intubation may be attended by fewer complications.

REFERENCES

1. Arens JF, Lejeune FE Jr, Webre DR: Maxillary sinusitis, a complication of nasotracheal intubation. Anesthesiology 40:415-416, 1974

2. Zwillich C, Pierson DJ: Nasal necrosis: a common complication of nasotracheal intubation. Chest 64:376-377, 1973

3. Berry FA Jr, Blankenbaker WL, Ball CG: A comparison of bacteremia occurring with nasotracheal and orotracheal intubation. Anesth Analg 52:873-876, 1973

SUCTION CATHETERS. This study was undertaken to evaluate mucosal trauma following tracheobronchial suctioning. Four different design suction catheters were evaluated including a beaded tip designed to prevent invagination of tracheal mucosa. The effect of a single suctioning procedure on the airway mucosa was observed and photographed through a fiberoptic bronchoscope. During a single suctioning procedure all catheters performed equally well and were associated with minimal trauma. Tracheal mucosal hemorrhage was not observed. Trauma with repeated suctioning is probably most related to frequency, vigor of catheter insertion, duration and negative pressure. *(Jung RC, Gottlieb LS: Comparison of tracheobronchial suction catheters in humans. Visualization by fiberoptic bronchoscopy. Chest 69:179-181, 1976)*

Supine Hypotensive Syndrome Caused by Intra-Abdominal Mass: A Case Report

JONG MIN KIM, MD*
CHANA BUAKHAM, MD†
FLORENCE McAMIS, RN‡
Kansas City, Kansas§

An obese woman who presented with 3 separate intra-abdominal masses developed a supine hypotensive syndrome following induction of general anesthesia. The hypotension was corrected by positioning the patient in a left lateral tilt and by releasing intra-abdominal pressure. Following decompression of the vena cava, arterial and central venous pressure rose and remained at a high level. Urine output was poor until IV furosemide was administered.

VENA CAVAL compression occurs in over 75 percent of normal term pregnancies, and 10 to 15 percent develop supine hypotensive syndrome.[1] Kennedy and associates[2] reported a 17.7 percent incidence of hypotension in normal vaginal deliveries under low spinal anesthesia. Left uterine displacement was effective in restoring blood pressure (BP) in 93.4 percent of these patients.

Eckstein and Marx[3] reported that elevation of the hip was more effective than mechanical displacement of the uterus in alleviating aortocaval compression. Evidently a large intra-abdominal mass can cause supine hypotensive syndrome similar to that caused by the near-term pregnant uterus.

REPORT OF A CASE

A 24-year-old obese woman, 156 cm in height and weighing 104 kg, was admitted with intrauterine pregnancy of 16 weeks gestation and an intra-abdominal mass. She had gained about 14 kg during her pregnancy and reported having had occasional cramping in hips and thighs, low back pain, episodes of coughing, and dyspnea upon minimal exertion. She denied the occurrence of dependent edema, varicosities, dizziness, or lightheadedness at any time during her pregnancy.

Preoperative laboratory data included: hemoglobin, 10.7 gm/100 ml; hematocrit, 32.9 percent, Na^+ 134; K^+ 3.8; Cl^- 103; and CO_2, 21 mEq/L. Chest x-ray and ECG were within normal limits. Sonography suggested a twin pregnancy and a large ovarian cyst extending into the upper abdominal cavity, measuring 17 x 15 x 15 cm. Despite 16 weeks gestation by history, the patient appeared as a full-term parturient, due to obesity and the intra-abdominal mass.

The patient was premedicated with 10 mg of diazepam and 0.5 mg of atropine, IM. Preoperative BP was 120/75, with a heart rate of 80/min. She was placed in low lithotomy position, 250 mg of thiopental and 80 mg of succinylcholine were administered, intubation was performed, and N_2O-O_2 (3.5:1.5) was started, with intermittent positive-pressure ventilation (IPPV). Following induction, her BP dropped to 60/40 and her heart rate rose to 120/minute. In spite of the hypotension, an additional dose of 75 mg of thiopental and 4 mg of pancuronium were administered to alleviate straining and coughing. The hypotension and tachycardia did not respond either to

*Assistant Professor.
†Assistant Professor.
‡Nurse Anesthesia Student.
§Department of Anesthesiology, University of Kansas Medical Center, Kansas City, Kansas 66103.

Paper received: 2/16/76
Accepted for publication: 3/1/76

increased fluid administration (1000 ml in 40 min) or to IV administration of 0.2 mg of phenylephrine given in 2 divided doses.

At this time, supine hypotensive syndrome was suspected, and the operating table was tilted to the left approximately 30 degrees. During the next 5 minutes, BP gradually rose to 110/50; heart rate remained elevated at 110/min. In an effort to determine if the hypotension was caused by vena caval compression, we restored the patient to the level position; this resulted in a BP drop to 80/60. As left lateral tilt was again resumed, the BP rose to 110/75 and remained stable until the peritoneum was opened, at which time her CVP was 3.5 cm H_2O.

The operation began 40 minutes after induction, with the patient in the left lateral tilt and low lithotomy position. She received 1000 ml of 5 percent dextrose in lactated Ringer's solution; during the same period, urine output was only 50 ml. Upon complete release of vena caval compression by opening the peritoneum, the BP and CVP rose to 150/90 and 17 cm H_2O, respectively, and heart rate fell to 100/min. The lateral tilt was removed without a change in either BP or heart rate.

In addition to a 16-week pregnant uterus, 2 large ovarian masses were found. The larger was a serous cystadenoma from the left ovary, measuring 15 x 20 x 20 cm; the smaller was a multilocular teratoma from the right ovary, measuring 10 x 10 x 12 cm. The left ovarian cyst was pushed into the upper abdominal cavity by the firm right ovarian teratoma and the pregnant uterus, and filled the entire epigastrium and upper abdominal cavity. Approximately 1500 ml of serous fluid was aspirated from the cystadenoma. Thereafter, BP and CVP stabilized at 140/90 and 14 cm H_2O, respectively.

Because of her high CVP and relatively poor urine output (175 ml for the 2-hour period, during which 1800 ml of fluid was given), 20 mg of furosemide was administered IV. This increased urine output from 175 to 1400 ml and decreased CVP to 7 cm H_2O, reduced BP from 140/90 to 110/60, and heart rate from 100 to 90/min within an hour.

The operation lasted 2.5 hours. Estimated blood loss was 1000 ml, replaced by the same amount of whole blood. Total fluid input was 2000 ml of 5 percent dextrose in lactated Ringer's solution. Anesthesia was maintained throughout with N_2O-O_2, supplemented with fractional doses of IV pancuronium (11 mg total dose) and fentanyl (0.3 mg total dose). The patient awoke in the operating room and the postoperative course was uneventful.

DISCUSSION

The clinical manifestations of vena caval compression by a pregnant uterus depend upon the degree of obstruction and the patient's ability to compensate. The mild decrease in venous return can be compensated by peripheral vasoconstriction and tachycardia without significant BP change. When these mechanisms become inadequate, supine hypotensive syndrome may develop, occasionally associated with bradycardia.[4] Compensatory mechanisms may be disturbed by either general or regional anesthesia.

In our patient, moderate vena caval compression by the intra-abdominal masses was well compensated preoperatively without significant clinical manifestations. However, when the intra-abdominal pressure was acutely raised by the tightening of the abdominal and thoracic muscles in the presence of inadequate muscle relaxation during induction of anesthesia, and venous return was impeded by IPPV, vena caval compression was acutely augmented. This impeded venous return beyond the patient's compensatory ability and was manifested as severe hypotension.

Rubinson and colleagues[5] demonstrated the marked narrowing of the inferior vena cava in dogs without significant change in arterial pressure when an inferior vena caval pressure gradient of 28 torr across the diaphragm was created by acute increase in intra-abdominal pressure. Further increase in intra-abdominal pressure to 35 to 40 torr resulted in a significant fall in arterial pressure. Lee[6] reported a patient who developed acute hypotension during laparoscopy when the intra-abdominal pressure reached 40 torr due to intraperitoneal CO_2 insufflation; BP returned to preoperative levels upon releasing intra-abdominal pressure.

When hypotension developed in our patient, fluid and vasopressor administration were not effective. Considering the overdistended abdomen and hypotension unresponsive to conventional therapy, we suspected the supine hypotensive syndrome. Left lateral tilt, with subsequent release of the intra-abdominal pressure upon opening the peritoneum, were effective in restoring blood pressure.

Epstein and Panter[7] described a patient in whom the arterial pressure and CVP rose following evacuation of a giant ovarian cyst, attributing the rise in BP and CVP to retained fluid distal to vena caval compression thrown into the systemic circulation. The initial BP and CVP elevations in our patient could be explained by a similar mechanism, but these pressures stayed high with relatively poor urine output. Furosemide decreased both and resulted in profuse diuresis. This suggested that decreased renal excretion of water, commonly associated with vena caval compression,[4] was not of postrenal origin. If postrenal obstruction was a causative factor, removal of the obstruction should increase urine output, as did rising BP.

Davis and colleagues[8] reported that when acute constriction of the proximal abdominal vena cava creates a sustained high venous pressure distally, aldosterone secretion is progressively elevated. Also, a smaller intra-arteriolar volume in the afferent arteriole of glomerulus stimulates the renin release.[9] In normal pregnancy, plasma renin activity and aldosterone concentration are increased.[10] The sodium-conserving effect appears about an hour after the IV administration of aldosterone.[11]

The time between induction of anesthesia to the opening of the peritoneum was about an hour. During that period, significant vena caval compression may have stimulated aldosterone and renin secretion, which had been increased by pregnancy. This could contribute to a sustained high CVP with relatively poor urine output.

REFERENCES

1. Little DM, Bonica J: Shock, Principles and Practice of Obstetrical Analgesia and Anesthesia. Edited by J Bonica. Philadelphia, FA Davis Company, 1969, p 1160

2. Kennedy RL, Friedman DL, Katchka DM, et al: Hypotension during obstetrical anesthesia. Anesthesiology 20:153-155, 1959

3. Eckstein KL, Marx GF: Aortocaval compression and uterine displacement. Anesthesiology 40:92-96, 1974

4. Kerr MG: The mechanical effects of the gravid uterus in late pregnancy. J Obstet Gynaecol Br Commonw 72:513-529, 1965

5. Rubinson RM, Vasko JS, Doppman JL, et al: Inferior vena caval obstruction from increased intra-abdominal pressure. Experimental hemodynamic and angiographic observations. Arch Surg 94:766-770, 1967

6. Lee CM: Acute hypotension during laparoscopy: a case report. Anesth Analg 54:142-143, 1975

7. Epstein RA, Panter GG: Giant ovarian cyst and the supine hypotensive syndrome. Anesthesiology 27:515-516, 1966

8. Davis JO, Kliman B, Yankopoulos A, et al: Increased aldosterone secretion following acute constriction of the inferior vena cava. J Clin Invest 37: 1783-1790, 1958

9. Oparil S, Haber E: The renin-angiotensin system (part I). N Engl J Med 291:389-401, 1974

10. Oparil S, Haber E: The renin-angiotensin system (part II). N Engl J Med 291:446-457, 1974

11. Haynes RC Jr, Larner J: Adrenocorticotropic hormone: adrenocortical steroids and their synthetic analogs: inhibitors of adrenocortical steroid biosynthesis, The Pharmacological Basis of Therapeutics. Fifth edition. Edited by LS Goodman, A Gilman. New York, The Macmillan Company, 1975, p 1483

TRIMETHAPHAN. The effect of trimethaphan produced hypotension (systolic blood pressure 60-65 torr) on blood glucose and serum potassium was measured in 10 patients. Anesthesia was with nitrous oxide-halothane and d-tubocurarine neuromuscular blockade. Compared with normotensive patients, those receiving trimethaphan manifested an attenuated hyperglycemic response and a small but significant decrease of serum potassium. These responses are mostly likely due to trimethaphan's ganglionic blocking properties. *(Fahmy NR: Changes in serum potassium and blood glucose concentrations after trimethaphan administration in man. J Lab Clin Med 87:999-1004, 1976)*

Twelfth Annual Becton, Dickinson and Company Oscar Schwidetzky Memorial Lecture

WILLIAM K. HAMILTON, MD

DR. WILLIAM K. HAMILTON, Professor and Chairman of the Department of Anesthesia, University of California, San Francisco, will deliver the 12th Annual Becton, Dickinson and Company Oscar Schwidetzky Memorial Lecture at the 51st Congress of the International Anesthesia Research Society, to be held at the Diplomat Resort and Country Club, Hollywood, Florida, March 6-10, 1977.

Widely known and admired among anesthesiologists, Bill Hamilton brings to our podium a unique blend of academic insight, clinical expertise, and personal common sense.

He was born and educated in Iowa and advanced from Clinical Instructor in Anesthesiology to Professor and Chairman of the Department of Anesthesiology at the University of Iowa in Iowa City. After nine years in the latter post, he moved to San Francisco in 1967 to assume his present duties and his second departmental chairmanship. Under his capable direction, the University of California Department of Anesthesia has continued its evolution into one of the most prominent clinical, educational, and research facilities in our specialty.

Included in Dr. Hamilton's busy schedule have been membership in many University of California School of Medicine committees, as well as such national posts as Past President of the American Board of Anesthesiology, membership on the Liaison Committee on Graduate Medical Education, membership on the Surgical Study Section A of the National Institutes of Health, and past presidencies of both the Association of University Anesthetists and the Society of Academic Anesthesia Chairmen. While this would completely preoccupy, if not overwhelm, most people, Bill Hamilton still finds time to participate in research and in daily clinical anesthesia. From such varied activities, he brings to his teaching efforts a blend of intellectual preparedness and clinical practicality that has won him respect from students and practitioners alike.

At the 51st Congress of this Society, Dr. Hamilton's topic will be "Pharmacology, Pressures and People."

The Fifteenth Annual Baxter-Travenol Lecture

ARTHUR C. GUYTON, MD

ARTHUR C. GUYTON, M.D., Professor and Chairman of the Department of Physiology and Biophysics at the University of Mississippi, will present the Fifteenth Annual Baxter-Travenol Lecture at the 51st Congress of the International Anesthesia Research Society, to be held at the Diplomat Resort and Country Club, Hollywood, Florida, March 6-10, 1977.

Long a leader in the fields of physiology and biophysics, Dr. Guyton is particularly recognized for his unique ability to reduce complex issues to simple diagrams and statements. His textbooks, embodying this attribute, have become major instructional assets to countless classes of students of various disciplines.

Dr. Guyton qualifies strongly as a "hometown boy," as he was born, educated through college (top honors at each level), and has subsequently taught in Oxford, Mississippi. However, he received his M.D. degree at Harvard Medical School (honors there also) and was exposed to the discipline of surgery at both Massachusetts General Hospital, and, during World War II, at the National Naval Medical Center. Since 1948, he has held his present post at the University of Mississippi Medical Center in Jackson.

A list of Arthur Guyton's awards, honors, and society offices reads like a roll call of available distinguished recognitions. Particularly noteworthy are a Presidential Citation (1956) for the development of aids for the handicapped; selection by the U.S. Junior Chamber of Commerce as one of the Ten Outstanding Young Men in America (1951); the Ross McIntyre Award for contributions to Medical Teaching and Research (1972); the Teaching Award of the Association of Chairmen of Departments of Physiology (1975); named lectureships of various specialty societies; presidencies and chairmanships of societies and committees; and editorial board activities on behalf of half a dozen scientific journals, including *Circulation Research* and the *American Journal of Physiology*.

The topic of Dr. Guyton's presentation to the 51st Congress of this Society will be "A Composite Analysis of Cardiovascular Regulation."

We Salute . . . .

Richard George Barton Gilbert, M.B., B.S., F.R.C.P.(C)

"Given a government with a big surplus and a big majority and a weak opposition, you would debauch a committee of archangels."—Sir John A. MacDonald, First Prime Minister of Canada.

A SON OF the Manse, which instilled patience, wit, and understanding, Dick Gilbert was educated at Haileybury College, England, and the University of London, graduating from St. Thomas' Hospital in 1933. These were lean years, but Dick devoted his postgraduate studies to internal medicine, then to anesthetics, at the Postgraduate Medical School, Hammersmith, followed by private practice prior to the outbreak of hostilities in Europe.

He served with distinction in the Second World War as a specialist in anesthetics in England, Northwest Europe, and in the Burma campaign in the Far East, retiring with the rank of Lieutenant Colonel in 1946. During these war years, he came in contact with the 3rd Canadian Division in Combined Operations, which influenced his decision to immigrate to Canada with his family in 1946.

From 1948 to the present, Dick has been clearly identified with McGill University, in Montreal. He had the good fortune of coming under the tutelage of two of the pioneers in Canadian anesthesia—Dr. Wesley Bourne and Dr. Harold Griffith. At the same time, he came under the persuasive spell of the late Dr. Wilder Penfield, noted neurosurgeon and founder of the Montreal Neurological Institute. From 1950, Dick devoted his energies to improving the science of neurological anesthesia, and from 1957 to 1970 as chairman of the university department, fostering postgraduate education and research in the specialty through the McGill Diploma Program and the autonomous Anaesthesia Research Department.

Dick has had the distinction of serving both the Society of Anaesthetists of Quebec and the Canadian Anaesthetists Society as President, and for many years acted as a wise and fatherly examiner for the Royal College of Physicians and Surgeons of Canada as well as the Quebec College. Following a sabbatical year at Montpellier University, in France, in 1970, Dick has continued in his post of Professor of Anaesthesia at McGill. Charismatic, always of good humor, Dick has been a counsellor to many and a friend to all in time of need, both here and abroad.

The Society is pleased to "Salute" Dick and his gracious wife, Eunice, and to wish them future health and happiness.

"Every man is a volume, if you know how to read him."—Channing.

Correspondence

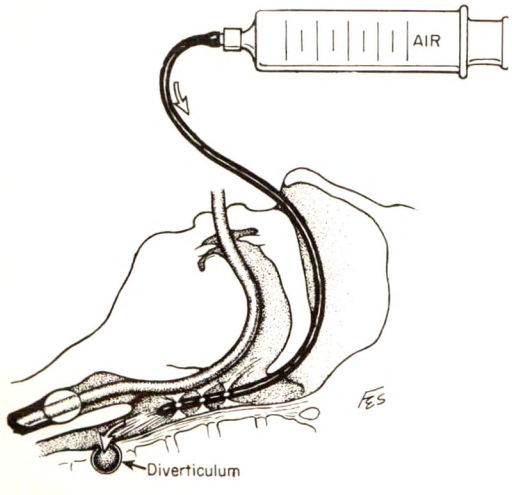
METHOD TO IDENTIFY A CERVICAL ESOPHAGEAL DIVERTICULUM DURING GENERAL ANESTHESIA

To the Editor:

Occasionally, the surgeon may have difficulty in identifying a small esophageal diverticulum during an operation under general anesthesia with a cuffed endotracheal tube properly placed. A simple maneuver that we have found effective is to pass a nasal catheter into the oropharynx (figure) and, after closing the lips and nostrils, gently introducing air. As the air pressure increases, the weak spot in the esophageal wall will distend and the diverticular sac can be seen as it expands into the operative field.

Although the illustration shows the air being introduced from a large syringe, one of us (MJN) prefers to blow his expired air into the catheter, as the pressure can be better evaluated and the potential usable volume is large enough to maintain a steady, small air pressure in the oropharynx.

It may be helpful to have the surgeon apply backward pressure on the cricoid cartilage, compressing the esophagus (Sellick maneuver) against the body of the vertebrae before introducing the air. This is not necessary if the operation is performed under cervical plexus block, for then the patient can be asked to swallow, thus increasing the oropharyngeal pressure, which will cause the diverticular sac to distend.



Morris J. Nicholson, MD
Frederick S. McAlpine, MD
Department of Anesthesiology
Lahey Clinic Foundation
Boston, Massachusetts

* * *

ACCURACY, BREVITY, CLARITY: THREE PRINCIPLES OF GOOD MEDICAL WRITING

To the Editor:

The article, "Righting the Wrongs of Writing: Copy Editors Speak Out," by Alexander and Wall,[1] contains some useful advice to authors, but one of the authors' final suggestions, "Write the way you talk," demands comment. This suggestion touches on a root cause of the low quality of medical writing that you, Sir, have done so much to correct by publishing helpful contributions concerning medical writing, such as Dr. Charles Roland's series, "Thoughts About Medical Writing"—and indeed the article by Alexander and Wall.

Alexander and Wall advise authors to write the way they talk. This is fine—provided authors talk well. But a fundamental reason why medical writing is frequently poor is precisely the fact that physicians write using words that they are comfortable with in communicating with their colleagues *orally*—and as a generalization, such words when printed lack effectiveness and interest. The corridor conversation and the grand rounds presentation are not a good basis for excellence in medical writing.

Alexander and Wall, in recommending

that authors should write the way they talk, also say that "people don't usually talk in five-syllable words." I disagree, if physician authors are included among such people. The trend in medical conversation or oral reporting is indeed toward use of polysyllabic words. Thus, the result of a physical examination may be said to be "noncontributory" (6 syllables), and "hepatosplenomegaly" (8 syllables) may or may not be said to be "nonsignificant" (five). Again, a patient may require "hospitalization" (six) because of "cardiorespiratory" (eight) "decompensation" (five). It is therefore not at all surprising that so many manuscripts submitted to medical journals are replete with benumbing polysyllabic words.

Good advice to authors is difficult to formulate, but Alexander and Wall have provided some helpful words of wisdom. It is more difficult to act on because writing is so personal and subjective an art. Writing, too, requires discipline, time, and hard work; and, as an editor, I sympathize with the busy physician who has to write when this is not necessarily a priority. What the physician therefore requires is the general assurance and understanding that to write well means that, in the long term, manuscripts take less time and effort to prepare —and may even be a pleasure to write. The physician author welcomes rules of thumb but to these must be added advice about the steps required in writing well.

Medical writing should seek to achieve what writing of any type should provide: effective communication between author and reader. True, the technical content of medical writing makes medical writing different from some other types of writing, but this should not deter the physician author; although great pains are required in order to select the right word so that the intended meaning is in fact conveyed, such care should come easily to anyone scientifically trained—and, in fact, such care is a plus because it makes for good rather than poor writing. With this in mind, one can offer 3 principles of good medical writing: accuracy, brevity, and clarity.

The need for *accuracy* should not surprise anyone, for "truth" is essential to all scientific work; and the description of a medical technic or the instructions relating to the administration of a drug *must* be accurate.

The need for *brevity* also should not surprise, though editors frequently receive manuscripts that are excessively long. But the adage, "Half as long is twice as good," is a useful one, not only because readers prefer to read short rather than long articles, but also because to be brief means to use simple and direct language. By cutting through the tangled undergrowth of redundancy, circumlocation, abstract terms, passive voice, and jargon, one avoids boring the reader and can set about interesting the reader instead.

And *clarity?* There is no shortcut to this *sine qua non* of writing, and one can only realize that, if one is to be sure of conveying one's message so that it is received, one must be clear. Clear thinking, a logical approach to organization, choice of the right word, relation of sentences to each other and of paragraphs to each other—these are the keys to clarity, but to achieve clarity one must be motivated to write well. Rules, then, are most helpful but help is required in their application.

How does one learn to write well? Recognition of the need to learn to improve one's skills is one step. A second step is motivation to learn—to learn through reading about writing, through attending workshops on writing such as those organized by, for example, the American Medical Writers Association, and through reading and studying the writing of good writers, particularly those who are known for their excellence of style. Only in this way can one become sensitized to what is good and what is poor. And the final step is to write, rewrite and write again, yet never to be completely satisfied. Writing well is an art that, like medicine, is a life-long one.

Communication is important in medicine, as it is in any field of social activity. Effective communication demands good writing, and, because so much of medical writing is technical in content and deals with the well-being of patients, the need for good medical writing is paramount. Good medical writing is not simply a virtue having its own reward; it may be an urgent need, as a recent case report showed.[2] In this instance a patient died after the labeling on a vial of chloramphenicol was misinterpreted. I agree therefore that "Righting the Wrongs of Writing" is an important matter, but I would like to emphasize that it is even more important at times than most of us realize.

David A. E. Shephard, MB, FRCP(C)
Scientific Editor
Canadian Medical Association Journal
Ottawa, Ontario, Canada

REFERENCES

1. Alexander JJ, Wall J: Righting the wrongs of writing: copy editors speak out (Editor's Choice). Anesth Analg 55:219-223, 1976

2. Thompson WL, Anderson SE, Lipsky JJ, et al: Overdoses of chloramphenicol. JAMA 234:149-150, 1975

* * *

WRITE TO INFORM, NOT TO IMPRESS

To the Editor:

I have been following the articles in Anesthesia and Analgesia on how to improve medical writing and after much rumination of the subject, I feel it is a love's labor lost.

Doctors write and speak the way they do with their consummate love for clichés and tautology because they can do nothing else. Nor do I think it is very important that they should.

Somerset Maugham points out in one of his essays that the greatest writers like Tolstoy or Joseph Conrad never mastered the technical aspects of the art of writing and that they made errors in composition such as a sophomore would never make.

We read the great writers not for their perfection of style or clarity of diction but for the stories they tell, the images they conjure up, for their philosophic asides, etc —not for their perfect grammar or composition.

Can it truly be claimed that if a new discovery tantamount to Jenner's vaccination were made, the world would not recognize or hasten to accept it because the discoverer's account included a cliché or a tautological expression? I doubt it.

Philip Eibel, MD
Ellendale Medical Bldg
Montreal, Quebec, Canada

* * *

USE OF MONITOR FOR KETAMINE IN RADIOTHERAPY

To the Editor:

In the description of their low-dose ketamine technic for radiotherapy,[1] Amberg and Gordon do not mention their monitoring equipment. We found[2] that viewing the patient through the observation port and closed-circuit television were inadequate and adapted conventional monitors to this special application. Perhaps the acceptance of their technic might be hastened by using one of the several monitors of pulse and respiration mentioned in our paper.

Alfred Feingold, MD
Department of Anesthesiology
University of Miami School of Medicine
Miami, Florida

REFERENCES

1. Amberg HL, Gordon G: Low-dose intramuscular ketamine for pediatric radiotherapy: A case report. Anesth Analg 55:92-94, 1976

2. Feingold A, Lowe HJ, Holaday DA, et al: Inhalation anesthesia and remote monitoring during radiotherapy for children. Anesth Analg 49:656-659, 1970

To the Editor:

Thank you for giving me an opportunity to reply to Dr. Feingold's letter.

During the course of treatment, we initially monitored the ECG via the observation port. We also took blood pressures while in the treatment room. After several treatments, we simplified this down to radial pulse monitoring and close observation of respiratory movements. We felt that one of the great advantages of ketamine was the preservation of protective reflexes, especially with the low dosages we were using. The other problem with placing multiple monitoring devices is the time factor. With low dosages and minimal pretreatment stress, placement of devices takes time away from treatment periods. With inhalation anesthesia, these monitoring devices are needed, but with low-dose ketamine, we feel they are not.

H. Lawrence Amberg, MD
Torrance, California

* * *

WHAT ROUTE OF ADMINISTRATION FOR K^+ SOLUTIONS?

To the Editor:

I cannot agree with Dr. Myron B. Laver's statement, "Potassium solutions must never be administered through a peripheral IV," which appeared in your March-April, 1976, issue.[1]

We all give potassium-containing solutions in peripheral veins every day (lactated Ringer's, Normosol-R, Ionosol B, etc). It

is true that solutions containing greater-than-physiologic concentrations of K^+ are most irritating to peripheral veins and must be given with care, but this does not preclude their being administered by this route. To insist, for instance, that a solution like Ionosol B (25/mEq L of K^+) be given through a central venous line would be submitting thousands of patients each day to the potential hazards of central venous catheterization. This would be a needless risk in most situations, and should remind us of the old caveat: *primum non nocere*.

Gary L. Fanning, MD
The McFarland Clinic
Ames, Iowa

REFERENCE

1. Laver MB: Questions and Answers. Anesth Analg 55:276, 1976

To the Editor:

Dr. Fanning is quite right in his criticism of the wording in my comment. It is true that solutions containing higher-than-physiologic concentrations of K^+ (in fact as high as 80 mEq/L or 0.08 mEq/L) have been and are being given into "peripheral" veins without apparent difficulty. He also states that substantially higher-than-physiologic (ie >0.005 mEq/ml) can cause "irritation" of peripheral veins.

However, what Dr. Fanning apparently has ignored is the fact that a number of patients, like the one in the query, may need substantial intravenous K^+ replacement before or during operation without the benefit of additional free water or electrolytes. For example, if a patient were to require a total of 100 mEq/L K^+ supplement, then according to Dr. Fanning's formula, using Ionosol B, one would have to administer no less than 4L of water plus other electrolytes. I do not consider this sound medical practice.

Careful reading of my answer to the question referred to will indicate that I suggested use of KCl, not "potassium-containing" solutions, for this purpose. What I did not state (and here Dr. Fanning is correct) is that these are *concentrated* solutions, mixed usually at 40 or 80 mEq/ml of K^+ with 5 percent glucose in water, in which case the K^+ concentration is 0.16 or 0.24 mEq/ml of K^+.

Whether this latter technic is to be used in an open ward or confined to an ICU or operating room is a different matter. The final decision must rest with the patient's physician. Acute changes in serum K^+ do occur with great frequency in the course of major operations. The method described is the one I prefer if intraoperative K^+ supplement is required.

The limitations as to hourly dosage still apply: 0.2 to 0.25 mEq/kg/hr K^+ and, without exception, these concentrated solutions must be administered via a central venous line. It is also good practice to include a commercially available graduated cylinder in the system (eg, Metriset®) and fill it only with the hourly dose of the K^+-containing solution, to prevent infusion of excessive quantities of the ion.

The manner in which K^+ supplementation is provided varies enormously. The success of commercially premixed solutions containing added K^+ suggests that in most cases it is an effective and safe mode of therapy. Unfortunately, there are situations in which this is convenient but not necessarily intelligent medicine. I wonder how Dr. Fanning would consider replacement in an elderly patient, in atrial fibrillation, on chronic digitalis therapy and not dehydrated who, prior to emergency operation, is found to have a K^+ of 2.5 mEq/L? How many liters of Ionosol B would it be safe to infuse peripherally to provide adequate K^+ replacement before his *primum non nocere* dictum becomes questionable?

Myron B. Laver, MD
Department of Anaesthesia
Massachusetts General Hospital
Boston, Massachusetts

To the Editor:

Thank you for sending me a copy of Dr. Laver's reply to my letter. A few additional comments are in order.

First of all, I did not state nor did I imply that Ionosol B should be used for the treatment of all K^+ deficiencies. I merely pointed to it as a fluid containing greater than physiologic concentrations of K^+ that is being given to thousands of patients every day via peripheral venous routes. Likewise, I did not state and did not mean to imply that all potassium-containing solutions should be given in peripheral veins. Obviously, there are many indications for using quite concentrated solutions of K^+, as pointed out by Dr. Laver, and these, I would

agree, are more properly given through a central venous catheter.

Gary L. Fanning, MD
The McFarland Clinic
Ames, Iowa

* * *

HOW DO BENEFITS OF HEMODILUTION BALANCE O_2 REDUCTION?

To the Editor:

The data from the recent paper by Gordon and associates,[1] regarding the effects of hemodilution on hypotension during cardiopulmonary bypass raise a disturbing issue on which the authors did not comment in their discussion: How does one balance the reputed benefits of hemodilution against the very real reduction in O_2 delivery to the patient that hemodilution must entail? I realize that Dr. Gordon's group did not set out to address this issue, but the degree of hemodilution they employed in several of their patients was of a magnitude that requires some justification by these gentlemen.

I have taken the information contained in table 2 of their article and rewritten it to express O_2 delivery per minute to the patient from the pump oxygenator (table). In making these calculations, I assumed that:

TABLE

Patient	Oxygen delivery in ml/min
1	370 ml/min
2	176
3	437
4	443
5	314
6	407
7	351
8	462
9	386
10	425
11	427
12	241
13	554
14	333
15	387
16	353
17	595
18	446
19	425
20	483

(1) hemoglobin (Hb) was fully saturated and had an O_2 binding capacity of 1.39 ml/gm; (2) a hematocrit of 3 percent corresponded to an Hb value of 1 gm/100 ml; (3) a body surface area was 1.8 sq m for all patients; and (4) that dissolved O_2 amounted to 1 ml/100 ml of blood.

Two patients would then have had a total O_2 delivery of less than 250 ml/min and 3 others would have received between 250 and 350 ml/min. Available O_2 is, of course, significantly less than this at 31° C. At this temperature, Hb is still 50 percent saturated at a PO_2 of 19 torr, and 25 percent saturated at 12 torr. Even assuming that O_2 requirements were reduced by a third at 31° C and still further by the anesthetic agents employed, it is unlikely that total O_2 consumption was much less than 150 ml/min. If the latter value is taken to be correct, patient 2 would have a mixed venous saturation of 17 percent and a mixed venous PO_2 of about 10 torr. Patient 12 would have a mixed venous saturation of 42 percent and a venous PO_2 of about 16 torr. The happy circumstance that both these patients apparently survived what can only be described as a severe physiologic challenge does not alter the fact that they were subjected to the risk of dangerously low reserves of O_2 for the very marginal benefits of reduced blood utilization and greater ease of perfusion.

Dr. Frank Gollan, in his discussion of this paper, concluded by noting that these patients did much better than theoreticians would have predicted, and that experimental and clinical evidence remain the guidelines for future work. I am afraid that I must respectfully disagree. The mere fact that one can "get away" with a theoretically unsound procedure is not sufficient justification for its use unless risk/gain advantages clearly argue in its defense.

Such is not the case here. Hemodilution to an Hb level of 4 gm/100 ml combined with only moderate hypothermia (30° C) and a perfusion level of 2.2 L/sq m represents a dangerous technic, and I believe Drs. Gordon and Ravin should say so.

Aaron F. Kopman, MD
Department of Anesthesiology
Long Island Jewish Hillside
Medical Center
New Hyde Park, New York

REFERENCE

1. Gordon RJ, Ravin M, Daicoff GR, et al: Effects of hemodilution on hypotension during cardiopulmonary bypass. Anesth Analg 54:482-487, 1975

To the Editor:

Dr. Gordon is in England, so I take the liberty of replying to the letter from Dr. Aaron Kopman in response to our article.

We would like to emphasize that the data referred to in table 2 of our paper apply only to the period immediately after the start of bypass. These abnormally low hematocrit values rapidly rose following a marked diuresis. It is also clear from table 1 that no special effort was made to induce hemodilution in patients 2 and 12; their pump primes are similar to those of the other 18 patients. The low hematocrit values following onset are clearly suggestive of hypovolemia. The degree of hypothermia we employed decreases O_2 need by approximately 50 percent. Finally, we are only making observations and not recommending any technic. But Dr. Kopman's analysis does indicate the importance of monitoring hemoglobin content during perfusion.

Mark B. Ravin, MD
Department of Anesthesiology
University of Kentucky
Medical Center
Lexington, Kentucky

* * *

EFFECT OF P_{aCO_2} ON O_2 CONSUMPTION DURING CARDIOPULMONARY BYPASS

To the Editor:

The recent paper by Patterson[1] on the effect of P_{aCO_2} on O_2 consumption during cardiopulmonary bypass, while otherwise well conceived, is, I am afraid, marred by a serious error in methodology.

In theory, the difference in O_2 content between arterial and mixed venous blood ($A\text{-}V_{DO_2}$) can be calculated from measured P_{O_2}, P_{CO_2}, pH, and hemoglobin (Hb). In practice, the results so obtained are not reliable for the following reasons:

The most serious problem with calculating Hb saturation and hence O_2 content from blood-gas determinations is that very small errors in the measurement of blood O_2 tension become greatly magnified as one goes along. If, for example, the $P\bar{v}_{O_2}$ is reported as 37 torr when it is in fact 5 torr higher, the calculated saturation will be 70 percent instead of 77 percent. Even assuming that arterial blood is fully saturated, this 5-torr error in the determination of mixed venous O_2 tension will result in almost a 25 percent error in the calculated $A\text{-}V_{DO_2}$.

Another potential source of trouble lies in assuming that the patient's O_2:Hb dissociation curve has a normal P_{50}. In the presence of prior anemia or blood transfusion, for example, considerable shifts in P_{50} can and do occur. Even after corrections are made for temperature, pH, and base excess, the actual value of P_{50} is subject to significant variation. An increase in P_{50} of only 2.5 torr is equivalent to a 10 percent increase in effective P_{O_2}.

Finally, the O_2-binding capacity of Hb may also vary by a considerable amount. While in theory, 1 gm of Hb carries 1.39 ml of O_2 when fully saturated, in practice this value is rarely achieved. DeVillota's group[2] found in normal subjects a mean value of 1.36 (range 1.33 to 1.41) for this parameter, while in heavy smokers the figure was 1.3 (range 1.21 to 1.41). Obviously, any arbitrary figure selected is likely to be wrong much of the time unless carboxyhemoglobin is also measured and accounted for.

If reliable values for $A\text{-}V_{DO_2}$ are to be obtained, O_2 content must be either measured volumetrically or calculated from measured Hb saturation, if the former is not feasible. It is, therefore, unfortunate that, while the author's data on O_2 consumption *may* be accurate, it is difficult to put much faith in the figures reported. I would very much like to see this study repeated with more rigorous attention to the problems discussed above.

Aaron F. Kopman, MD
Department of Anesthesiology
Long Island Jewish-Hillside
Medical Center
New Hyde Park, New York

REFERENCES

1. Patterson RW: Effect of P_{aCO_2} on O_2 consumption during cardiopulmonary bypass in man. Anesth Analg 55:269-273, 1976

2. DeVillota ED, Carmona MTG, Barat G, et al: The influence of carboxyhemoglobin on the oxygen binding capacity of blood. Br J Anaesth 48:111-117, 1976

To the Editor:

Thank you for relaying Dr. Kopman's letter to me.

In reply:

In the preparation of the table of results, it was not obvious that there was a need to

tabulate all of the arterial and mixed venous blood-gas values. Had this been done, it would have been apparent from the tension decreases as CO_2 was added that an increased quantity of O_2 was being removed even though the total O_2-carrying capacity may have been constantly impaired.

Contributing to the belief that changes in $\dot{V}O_2$ were actually occurring were the findings that essentially the same results were obtained whether, from the initial state, CO_2 was added or subtracted; the fact that the trend of the changes was similar regardless of the absolute constant temperature during the study; and also, though not a part of the study, when the same bypass occurred for long periods at 2 different temperatures, $\dot{V}O_2$ was markedly higher at the higher temperature.

Dr. Kopman is correct in pointing out that in precisely deriving content from tension, total O_2-carrying capacity and Hb:O_2 affinity must be known. Dissatisfaction with the available methods of calibrating the co-oximeter (as well as the variability in the calculated factors, also mentioned in the last paragraph of the paper by DeVillota), precluded a systematic evaluation of carboxyhemoglobin (COHb) in this study.

However, the range of COHb values to be expected during our study conditions is indicated by a separate study, where we measured COHb spectrophotometrically. Immediately prior to commencing bypass, patient COHb averaged less than 3 percent. Sampling the initial pump prime disclosed a wide range of values, 2.2 to 6.5 percent. There was a progressive decline in COHb during bypass; at the end of 1 hour, the average value was <2 percent.

Since actual volumetric measurements of O_2 consumption on a minute-to-minute basis show a 6 to 10 percent coefficient of variation around a mean steady-state value, it was considered that the assumptions made in this study contributed to a lesser percentage of error in $\dot{V}O_2$ estimation than that inherent, in that the overall average value may differ from the discrete value of a particular sampling period. More precise values for $\dot{V}O_2$ during bypass can be obtained by adapting the method of measuring $\dot{V}O_2$, which we are currently using in patients in situations where collection of all expired gas is feasible (with subsequent analysis of inspired and expired respiratory gases by mass spectrometry and minute-to-minute on-line computation of $F_{E}N_Z/F_{I}N_Z$, RQ, and $\dot{V}O_2$); steady-state conditions are clearly designated, and the requirement of measuring P_{50} and the O_2-carrying capacity of Hb is obviated.

Thank you again for your continuing interest. From the large number of reprint requests, we believe that perhaps others will be stimulated to look more closely at some of the circulatory changes occurring during bypass.

Richard W. Patterson, MD
Department of Anesthesiology
UCLA
Los Angeles, California

CORRECTION

The illustration accompanying the *Correspondence* item entitled "Plastic-Covered Wire Stylet," which appeared on page 755 of the September-October issue was incorrect. The correct illustration is:

In each issue of the Journal an article of particular interest and value to anesthesiologists, which has been published elsewhere, will be presented. Primarily the material will contain fundamental basic information which has been presented by anesthesiologists, physiologists, pharmacologists, and others and, on occasion, by commercial firms. In the last instance, these reprintings are not to be construed as an endorsement of the particular commercial firm or its product by Anesthesia and Analgesia—Current Researches.

Retrospectroscope . . . the Soul of Wit

ABRAHAM LINCOLN, on November 19, 1863, delivered his Gettysburg Address, one of the most elegant, famous, and widely quoted of modern speeches. Delivered on a Civil War battlefield, it was almost finished before the crowd became quiet. Few in the audience heard all or much of it. The Address contained only 272 words and, in print, was a single paragraph.

As a schoolboy, I (and I suppose all school-children throughout America) memorized Lincoln's Address and recited it in the classroom. Never in my later scientific training, however, has anyone ever suggested that I memorize and recite a scientific article. I'm sure no candidate-article was as eloquent as Lincoln's Address, but some important discoveries or concepts were presented about as briefly. Here are a few; they include only complete accounts that stood alone and not abstracts that were enlarged upon later in a full article.

Benjamin Franklin, foremost scientist in the American Colonies, communicated in a one-page letter (one paragraph, 342 words, excluding his salutation) the details and conclusions of his famous kite and key experiment by which he demonstrated for the first time the "sameness" of lightning and "electric matter" stored in a Leyden jar (figure 1).

Korotkoff, in 1905, wrote a single paragraph describing how he modified Riva-Rocci's method to permit measurement of diastolic blood pressure and accurate recording of systolic pressure; his 1905 technic is essentially that used today. This paragraph is all that Korotkoff ever published on the subject (267 words in the English translation):

ON THE SUBJECT OF METHODS OF DETERMINING BLOOD PRESSURE

(From the clinic of Prof. S. P. Fedorov)

DR. N. S. KOROTKOFF:

On the basis of his observations, this reporter has arrived at the conclusion that a completely compressed artery in a normal condition does not produce any sound. Taking advantage of this situation the reporter proposes the sound method for determining the blood pressure in humans. The sleeve [cuff] of Riva-Rocci is placed on the middle 1/3 of of the arm toward the shoulder. The pressure in the sleeve is raised quickly until it stops the circulation of the blood beyond the sleeve. Thereupon, permitting the mercury manometer to drop, a child's stethoscope is used to listen to the artery directly beyond the sleeve. At first no audible sound is heard at all. As the mercury manometer falls to a certain

Reprinted with permission from American Review of Respiratory Disease and the author.

Oct. 19, 1752.

AS frequent mention is made in the news papers from *Europe*, of the ſucceſs of the *Philadelphia* experiment for drawing the electric fire from clouds by means of pointed rods of iron erected on high buildings, *&c.* it may be agreeable to inform the curious that the ſame experiment has ſucceeded in *Philadelphia*, though made in a different and more eaſy manner, which is as follows:

Make a ſmall croſs of two light ſtrips of cedar, the arms ſo long as to reach to the four corners of a large thin ſilk handkerchief when extended; tie the corners of the handkerchief to the extremities of the croſs, ſo you have the body of a kite; which being properly accommodated with a tail, loop, and ſtring, will riſe in the air, like thoſe made of paper; but this being of ſilk is fitter to bear the wind and wet of a thunder guſt without tearing. To the top of the upright ſtick of the croſs is to be fixed a very ſharp pointed wire, riſing a foot or more above the wood. To the end of the twine, next the hand, is to be ty'd a ſilk ribbon, and where the ſilk and twine join, a key may be faſtened. This kite is to be raiſed when a thunder guſt appears to be coming on, and the perſon who holds the ſtring muſt ſtand within a door, or window, or under ſome cover, ſo that the ſilk ribbon may not be wet; and care muſt be taken that the twine does not touch the frame of the door or window. As ſoon as any of the thunder clouds come over the kite, the pointed wire will draw the electric fire from them, and the kite, with all the twine, will be electrified, and the looſe filaments of the twine will ſtand out every way, and be attracted by an approaching finger. And when the rain has wet the kite and twine, ſo that it can conduct the electric fire freely, you will find it ſtream out plentifully from the key on the approach of your knuckle. At this key the phial may be charged; and from electric fire thus obtained, ſpirits may be kindled, and all the other electric experiments be performed, which are uſually done by the help of a rubbed glaſs globe or tube; and thereby the ſameneſs of the electric matter with that of lightening completely demonſtrated.

B. F.

height the first short tones appear, the appearance of which indicates the passage of part of the pulse wave under the sleeve. Consequently, the manometer reading at which the first tones appear corresponds to the maximum pressure. With a further fall of the mercury in the manometer systolic pressure murmurs are heard which change again to a sound (secondary). Finally, all sounds disappear. The time at which the sounds disappear indicates a free passage of the pulse wave; in other words, at the moment the sounds disappear, the minimum blood pressure in the artery exceeds the pressure of the sleeve. Consequently, the reading of the manometer at this time corresponds to the minimum blood pressure. Experiments on animals gave positive results. The first sound-tones appear (10-12 mm) sooner than the pulse, for the perception of which (r. art. radialis) the breakthrough of a greater part of the pulse wave is required.

Cooke and Barcroft, in 1913, recorded the first measurement of O_2 saturation of human arterial blood (four paragraphs, but only 180 words). Although Hürter had performed arterial puncture in Germany a year earlier, Barcroft took advantage of the then-current clinical technic for transfusion (inserting a cannula into the donor's artery and running arterial blood directly into the recipient's vein) to obtain blood without exposure to air or contamination with anesthetic gases. A year later, Hustin in Belgium hit upon citrate as a safe anticoagulant and indirect transfusions of venous blood replaced the artery-to-vein technic. Widespread use of arterial puncture for diagnostic purposes or physiologic investigation didn't surface until World War II.

Adolph Fick (1870) wrote only two paragraphs on the measurement of cardiac output; in the first, he outlined his principle, and in the second, gave a sample calculation based on reasonable data:

> Herr Fick had a contribution on the measurement of the amount of blood ejected by the ventricle of the heart with each systole, a quantity the knowledge of which is certainly of great importance. Varying opinions have been expressed on this. While Thomas Young estimated the quantity at about 45 cc, most estimates in modern textbooks, supported by the views of Volkmann and Vierordt, run much higher, up to 180 cc. It is surprising that no one has arrived at the following procedure by which this important value is available by direct determination, at least in animals. One measures how much oxygen an animal absorbs from the air in a given time, and how much CO_2 it gives off. One takes during this time a sample of arterial and a sample of venous blood; in both samples oxygen content and CO_2 content are measured. The difference of oxygen content gives the amount of oxygen each cubic centimeter of blood takes up in its passage through the lungs; and as one knows how much total oxygen has been taken up in given time, one can calculate how many cubic centimeters of blood have passed through the lungs in this time, or if one divides by the number of heartbeats during this time, how many cubic centimeters of blood are ejected with each beat. The corresponding calculation with CO_2 quantities gives a determination of the same value, which provides a control for the other calculation.
>
> Since for the demonstration of this method two gas pumps are needed, your reporter unfortunately is not in a position to communicate experimental data. He will only give, therefore, a calculation of blood flow in man according to this method, based on more or less arbitrary data. According to the experiments of Scheffer in Ludwig's laboratory, dog's arterial blood contains 0.146 cc oxygen per cc (measured at 0° C and 1 atm pressure); 1 cc of venous blood contains 0.0905 cc oxygen. Each cc of blood therefore takes up 0.0555 cc oxygen in its passage through the lungs. Let us assume the same in man. Assume, further that a man absorbs in 24 hours 833 grams of oxygen. This will occupy a space of 433,200 cc at 0° C and 1 atm pressure. According to this, 5 cc of oxygen would be absorbed by the lungs of a man each second. In order to effect this absorption, 5/0.0555 cc of blood must perfuse the lungs per second, that is, 90 cc. Assuming, finally, 7 systoles in 6 seconds, each systole would then eject 77 cc of blood.

Note Fick's statement that "It is surprising that no one has arrived at the following procedure by which this important value is available by direct determination," but he did no experiments because he had no "gas pumps" for measuring the O_2 or CO_2 content of blood. The first experimental determination based on his principle was reported 16 years later by Gréhant and Quinquaud (in a one-page paper); they reported measurements in 6 dogs.

William Dock in 1929 adapted the then-new cathode ray oscillograph to monitor and to record ECG (229 words); the CRO monitor is now routine in all operating rooms and intensive care units and, as such, is quite familiar to avid TV viewers.

Others who reported important discoveries in one page or less were the following:

Faraday (1818), who reported that inhalation of ether vapor produced effects similar to those of nitrous oxide.

O'Shaughnessy (1832), who discovered severe fluid and electrolyte disturbances in patients with cholera; within a year his work led to the first rational therapy of this scourge by Latta.

Pasteur (1882), who recounted his successful vaccination of sheep against anthrax; 100 percent of those not vaccinated died, while 100 percent of those vaccinated up to 8 months previously lived.

Hektoen (1907), who suggested that mixing blood of donor and recipient and examining the mixture for agglutinated red blood cells could eliminate transfusion reactions.

Carrel (1911), who described his technic of repeatedly passing tissue fragments cultured *in vitro* from an old to a fresh medium; this technic later became important in many fields, particularly in the culture of polio virus and preparation of polio vaccine.

Guthrie (1919), who demonstrated that blood vessels do not survive as such when transplanted from one animal to another but do provide a scaffolding or bridge for ingrowth of new tissue derived from the host.

Joliot and Curie (1934), who first announced the transmutation of one element to another (the alchemist's dream). They changed boron, magnesium, and aluminum into radionitrogen, radiosilicon, and radiophosphorus, respectively, and won a third Nobel Prize for the Curie family.

Alvarez and Cornog (1939), who first produced tritium in the Berkeley cyclotron.

Pattle (1955), who observed stable pulmonary edema foam and speculated that the surface tension of lung bubbles is zero.

Lehmann (1946), who noted that pathogenic tubercle bacilli have an increased uptake of O_2 in the presence of salicylates and first used para-amino salicylic acid as a bacteriostatic agent against tubercle bacilli.

Somewhat more verbose were the following:

- *Hooke* (1667), who required a page-and-a-half to present proof that rhythmic movements of the lung were not necessary for life if the lungs were inflated by a stream of air (figure 2). Hooke missed the one-page-or-less category because he also included in his article a bit about artificial ventilation, a technic for continuous positive airway pressure (though scarcely applicable clinically because he pricked the outer layer of the lungs with the "slender point of a very sharp penknife" to maintain a continuous flow of air *through* the alveoli), proof that pulmonary blood flow without ventilation could not maintain life and a suggestion that extracorporeal oxygenation of blood was feasible (really *aeration,* since there was no oxygen in 1667).

Henry (1803), who required two pages to present his law relating partial pressure of a gas in a liquid to the quantity dissolved in it.

Von Behring and Kitasato (1890), who needed one-and-a-half pages to tell the medical world of immunization against diphtheria and tetanus; they were awarded the Nobel Prize in 1901 for this work.

Curie, Curie, and Bémont (1898), who used two-and-a-half pages to announce the discovery of radium in pitchblende (another Nobel Prize-winning discovery).

Hering (1924), who took two pages to describe the carotid sinus reflex.

Bayliss and Müller (1928) who needed two pages to describe and illustrate their rotary, roller pump, later known by a variety of names, such as the DeBakey pump (three pages).

Urey, Brickwedde, and Murphy (1932), who used one-and-a-half journal pages to announce the preparation of deuterium.

Stanley (1935), who needed one-and-a-half pages to announce the isolation from infected tobacco plants of a crystalline protein with the properties of tobacco-mosaic virus.

Enders, Weller, and Robbins (1949), who expended one-and-three-quarter pages to present the cultivation of polio virus in human embryonic tissue, which led to the Nobel Prize for them and polio vaccine for all.

Clements (1957), who took one-and-a-half pages to quantify the surface-tension lowering properties of pulmonary surfactant ("anti-atelectasis factor").

Some wrote very long articles that are known today largely for a single paragraph. Henry Head's 70-page paper "On the regulation of respiration" (1889) is remembered mainly for one paragraph on page 13, in which he parenthetically described "Head's paradoxical reflex." And Christian Bohr's 33-page paper (1891) is remembered by most for his equation for respiratory dead space, stated in a few lines on page 248.

It's pretty hard nowadays to join this very select club of those who have written (and had published) a very short, important paper. You can try but I doubt that you'll succeed. Editorial boards resist accepting either long papers or very short papers (unless the latter are carefully segregated in a special section, suggesting that they are

An Account
*of an Experiment made by M.*Hook, *of Preſerving Animals alive by Blowing through their Lungs with Bellows.*

I Did heretofore give this *Illuſtrious Society* an account of an Experiment I formerly tryed of keeping a Dog alive after his *Thorax* was all diſplay'd by the cutting away of the *Ribbs* and *Diaphragme*; and after the *Pericardium* of the Heart alſo was taken off. But divers perſons ſeeming to doubt of the certainty of the Experiment (by reaſon that ſome Tryals of this matter, made by ſome other hands, failed of ſucceſs) I caus'd at the laſt Meeting the ſame Experiment to be ſhewn in the preſence of this *Noble Company*, and that with the ſame ſucceſs, as it had been made by me at firſt; the Dog being kept alive by the Reciprocal blowing up of his Lungs with *Bellowes*, and they ſuffered to ſubſide, for the ſpace of an hour or more, after his *Thorax* had been ſo diſplay'd, and his *Aſpera arteria* cut off juſt below the *Epiglottis*, and bound on upon the noſe of the Bellows.

And becauſe ſome Eminent Phyſitians had affirm'd, that the *Motion of the Lungs* was neceſſary to Life upon the account of promoting the Circulation of the Blood, and that it was conceiv'd, the Animal would immediately be ſuffocated as ſoon as the Lungs ſhould ceaſe to be moved, I did (the better to fortifie my own *Hypotheſis* of this matter, and to be the better able to judge of ſeveral others) make the following additional Experiment; *viz.*

The Dog having been kept alive, (as I have now mentioned) for above an houre, in which time the Tryal had been often repeated, in ſuffering the Dog to fall into *Convulſive* motions by ceaſing to blow the Bellows, and permitting the Lungs to ſubſide and lye ſtill, and of ſuddenly reviving him again by renewing the blaſt, and conſequently the motion of the Lungs: This, I ſay, having been done, and the Judicious Spectators fully ſatisfied of the reallity of the former Experiment; I cauſed another pair of Bellowes to be immediately joyn'd to the firſt, by a contrivance, I had prepar'd, and pricking all the outer-coat of the Lungs with the ſlender point of a very ſharp pen-knife, this ſecond pair of Bellows was mov'd very quick, whereby the firſt pair was alwayes kept full and alwayes blowing into the Lungs; by which means the Lungs alſo were alwayes kept very full, and without any motion; there being a continual blaſt of Air forc'd into the Lungs by the firſt pair of Bellows, ſupplying it as faſt, as it could find its way quite through the Coat of the Lungs by the ſmall holes pricked in it, as was ſaid before. This being continued for a pretty while, the Dog, as I exſpected, lay ſtill, as before, his eyes being all the time very quick, and his Heart beating very regularly: But, upon ceaſing this blaſt, and ſuffering the Lungs to fall and lye ſtill, the Dogg would immediately fall into Dying convulſive fits; but be as ſoon reviv'd again by the renewing the fulneſs of his Lungs with the conſtant blaſt of freſh Air.

Towards the latter end of this Experiment a piece of the Lungs was cut quite off; where 'twas obſervable, that the Blood did freely circulate, and paſs thorow the Lungs, not only when the Lungs were kept thus conſtantly extended, but alſo when they were ſuffer'd to ſubſide and lye ſtill. Which ſeem to be Arguments, that as the *bare* Motion of the Lungs *without freſh Air* contributes nothing to the life of the Animal, he being found to ſurvive as well, when they were not mov'd, as when they were; ſo it was not the ſubſiding or moveleſneſs of the Lungs, that was the immediate cauſe of Death, or the ſtopping the Circulation of the Blood through the Lungs, but the *want* of a ſufficient *ſupply of freſh Air*.

I ſhall ſhortly further try, whether the ſuffering the Blood to circulate through a veſſel, ſo as it may be openly expoſed to the freſh Air, will not ſuffice for the life of an Animal; and make ſome other Experiments, which, I hope, will throughly diſcover the *Genuine uſe of Reſpiration*; and afterwards conſider of what benefit this may be to Mankinde.

grade B and not grade A contributions). I suspect that today some of those mentioned earlier in this article would have received letters from the editor such as these:

Dear Dr. Korotkoff:

Thank you for permitting us to read your interesting manuscript. We regret that we cannot publish it in its present form. You may wish to resubmit it after you have (1) compared data obtained by your method with that obtained by the Riva-Rocci method in a large number of subjects of different ages and different arm circumferences, (2) verified the accuracy of your method against direct measurements of systolic and diastolic arterial blood pressure in animals, and (3) done statistical analysis of the data.

Sincerely,
The Editors

Dear Professor Fick:

Thank you for sending us your interesting suggestion for measuring cardiac output. We regret that we do not publish ideas unsupported by data and are returning your paper forthwith.

Sincerely,
The Editors

Dear Dr. Hooke:

We have read your communication entitled "Preserving animals alive by blowing through their lungs with bellows." We note that you have been sending us a number of short communications, none of which has been suitable for publication. We suggest that you consider combining all of these into one longer, more substantial manuscript that might contain enough new information to make it worthy of acceptance.

Respectfully,
The Editors

JULIUS H. COMROE, JR.

REFERENCES

Alvarez LW, Cornog R: Helium and hydrogen of mass 3. Phys Rev 56:613, 1939

Bayliss LE, Müller EA: A simple high-speed rotary pump. J Sci Instr 5:278-279, 1928

von Behring EA, Kitasato S: Ueber das Zustandekommen der Diptherie-Immunität und der Tetanus-Immunität bei Thieren, Dtsch Med Wochenschr, 16: 1113-1114, 1890

Bohr C: Ueber die Lungenathmung. Skand Arch Physiol, 2:236-268, 1891

Carrel A: Rejuvenation of cultures of tissues. JAMA 57:1611, 1911

Clements, JA: Surface tension of lung extracts. Proc Soc Exp Biol Med 95:170-172, 1957

Cooke A, Barcroft J: Direct determination of the percentage saturation of arterial blood with oxygen in a normal person. J Physiol 47:xxxv, 1913

Curie P, Curie M, Bémont G: Sur une nouvelle substance fortement radio-active, contenue dans la pechblende. C R Acad Sci 127:1215-1217, 1898

Dock W: The use of the cathode ray oscilloscope for electrocardiography. Proc Soc Exp Biol Med 24:566, 1929

Enders JF, Weller TH, Robbins FC: Cultivation of the Lansing strain of poliomyelitis virus in cultures of various human embryonic tissues. Science 109:85-87, 1949

Faraday M: Effects of inhaling the vapour of sulphuric ether. J Sci Arts 4:158-159, 1818

Fick A: Über die Messung des Blutquantums in den Herzventrikeln. S B Phys-Med Ges Würzburg xvi, July 9, 1870

Franklin B: New Experiments and Observations on Electricity Made at Philadelphia in America, ed 3, part I, D Henry and R Cave, London, pp 106-108, 1760

Guthrie CC: End-results of arterial restitution with devitalized tissue. JAMA 73:186-187, 1919

Head H: On the regulation of respiration. J Physiol 10:1-70, 1889

Hektoen L: Isoagglutination of human corpuscles. JAMA 48:1739-1740, 1907

Henry W: Experiments on the quantity of gases absorbed by water, at different temperatures, and under different pressures. Proc R Soc Lond, 1:103-104, 1803

Hering HE: Die Änderung der Herzschlagzahl durch Änderung des arteriellen Blutdruckes erfolgt auf reflektorischem. Wege, Pflügers Arch 206:721-723, 1924

Hooke R: An account of an experiment made by M Hook[e], of preserving animals alive by blowing through their lungs with bellows. Philos Trans R Soc Lond 2:539-540, 1667

Joliot F, Curie I: Artificial production of a new kind of radio-element. Nature 133:201-202, 1934

Korotkoff NS: K voprosu metodakh uzsledovaniya krovanovo devleniya. Voen Med Akad Izvestiia. 11:365, 1905. Translated by AS Badger. Cardiovasc Res Cent Bull. vol 5:57-74, 1967

Lehmann J: Determination of pathogenicity of tubercle bacilli by their intermediate metabolism. Lancet 1:14-15, 1946. Para-aminosalicylic acid in the treatment of tuberculosis. Ibid, 15-16

O'Shaughnessy WB: Experiments on the blood in cholera. Lancet 1:490, 1831-1832

Pasteur L: Sur des experiences de vaccination charbonneuse. Bull Seances Soc Agr France 42:74-75, 1882

Pattle RE: Properties, function, and origin of the alveolar lining layer. Nature 175:1125-1126, 1955

Stanley WM: Isolation of a crystalline protein possessing the properties of tobacco-mosaic virus. Science 81:644-645, 1935

Urey HC, Brickwedde FG, Murphy GM: A hydrogen isotope of mass 2. Phys Rev 39:164-165, 1932

The Physician & The Law

Informed Consent Suit Against Anesthesiologist

A TRIAL court's decision in favor of an anesthesiologist should be reversed because the court failed to instruct the jury on the anesthesiologist's duty to inform the patient of risks inherent in treatment, the Vermont Supreme Court ruled. The case was remanded for a new trial.

The patient underwent surgery. Halothane was used as the general anesthetic. Later, the patient developed what was diagnosed as halothane hepatitis. Claiming she had not been informed of the possibility of hepatitis when she consented to the surgery, she brought an action against the anesthesiologist. A jury found in favor of the anesthesiologist, and the patient appealed.

The Vermont Supreme Court said that the trial court's instruction to the jury was too restrictive. The jury had been instructed that the anesthesiologist must disclose risks to the patient according to prevailing medical practice in the community. The supreme court stated that a physician must give a patient all information material to the decision to undergo the proposed treatment. The standard by which materiality is measured is the significance that a reasonable person would attach to the risks involved.

The real dispute in the case involved whether there was such a condition as halothane hepatitis, the court said. Evidence was introduced to show that there was not, and consequently there was no duty to warn of it. The possibility of halothane sensitivity was also disputed. Medical testimony indicated that the patient's condition was probably part of a postoperative depression due to the bilateral mastectomy plus a flare-up of her chronic colitis.

An osteopath who examined her initially diagnosed her condition as having its source in her colitis and not her liver. He later changed his mind after reviewing medical literature and material on halothane. Although it was the first time he had ever made such a diagnosis, he concluded that her condition was halothane hepatitis. Testimony indicated that the symptoms were non-specific and could have been caused by colitis or surgical trauma.

The anesthesiologist testified that he had not informed the patient of the possibility of halothane hepatitis. Under Vermont case law, if a reasonable person would not have consented to the operation had he been informed of the risk of halothane hepatitis, then the anesthesiologist was negligent for not furnishing the information.

The trial court's judgment was reversed and the case remanded for a new trial.—*Small v. Gifford Memorial Hospital,* 349 A.2d 703 (Vt.Sup.Ct., Nov. 24, 1975)

Reprinted by permission from THE CITATION, published by the Law Division of the American Medical Association.

Questions and Answers

We invite you to submit questions to the Editorial Office, Kahler East, Suite C, Rochester, Minnesota 55901. The names of those submitting questions will remain anonymous if so desired.

The answers will be prepared by competent authorities, and their names will or will not appear, according to their specific wishes.

Ronald W. Dunbar, M.D.
Contributing Editor
Atlanta, Georgia

* * *

QUESTION: *My question concerns "balanced anesthesia," about the interpretation of which we are having differences of opinion in the Anesthesia Department. May I ask you to give the proper definition of this term? Also, which agents do you feel are usually combined during the use of this type of anesthesia (including different inhalation, as well as intravenous and intramuscular agents).*

The point in question here is whether two or more agents generally considered strong anesthetic agents each in its own right (such as enflurane, methoxyflurane, halothane, and/or ether) can be used simultaneously, mixed with N_2O and O_2, in low concentrations. Would this be considered, academically speaking, an accepted procedure in giving "balanced anesthesia?"

MD, Korea

ANSWER #1: The term, "balanced anesthesia," has no strict definition and thus has been used to describe many different drug combinations. Nevertheless, balanced anesthesia most often denotes anesthetic maintenance with N_2O plus neuromuscular blockers and supplementation with injectable but not with potent inhalation anesthetic drugs. The logic for considering a N_2O-narcotic-barbiturate-relaxant combination a balanced anesthetic, while not applying the same label to anesthetic maintenance with N_2O-halothane-relaxant, is not sound. Ideally, anesthetic drugs should be used in doses sufficient to produce desirable responses such as amnesia and analgesia, while neuromuscular blockers provide appropriate skeletal-muscle relaxation. Thus, neuromuscular blockers are not used to cover inadequate doses of anesthetic drugs nor should excessive concentrations of depressant drugs be used in attempts to produce profound muscle relaxation.

It would seem logical to abandon the term "balanced" to denote some undefinable anesthetic technic or drug combination. Instead, one should state the drugs used for anesthetic maintenance in each patient. True balanced anesthesia is the concept of drug use to obtain maximal beneficial effects with minimal undesirable responses. Thus, anesthetic maintenance with appropriate doses of either inhalation and/or injectable anesthetic agents, with or without neuromuscular blockers, represents balanced anesthesia.

Robert K. Stoelting, MD
Department of Anesthesia
Indiana University School
of Medicine
Indianapolis, Indiana

ANSWER #2: My experience and contacts in anesthesia for many years would indicate that rarely would the mixture of inhalation anesthesia agents, as suggested in the question, be what would come to the mind of most anesthesiologists as associated with the term "balanced anesthesia." Certainly to give these agents together is an acceptable procedure, but as to whether reference to same as "balanced anesthesia" is usual and customary, I would have to say possibly such usage would create a false impression. I have been unable to decide from the literature who first referred to "balanced anesthesia," (possibly John Lundy) but the common use of the term was, and is, most often associated with thiopental, N_2O, and a relaxant, either with or without a narcotic

added. Now many other drugs are used or added to the basic mixture. Any combination of drugs that in the hands of the individual administrator gives the desired anesthetic effect and does so in a physiologically benign manner and permits restoration of the preanesthetic state rapidly is a "balanced anesthetic." While the last point of the questioner is unanswered by this, it can be stated that the practice described is acceptable and commonplace anywhere and may be called whatever seems appropriate to the anesthesiologist.

Roy D. Wilson, MD
Department of Anesthesiology
Baylor College of Medicine
Houston, Texas

CONTINUOUS POSITIVE AIRWAY PRESSURE. The noninvasive use of continuous positive airway pressure (CPAP) avoids the hazards of tracheal intubation. Arterial blood gases were determined before and after CPAP in 14 patients in acute respiratory distress. Criteria for CPAP were an ability to follow commands, $PaCO_2$ <45 torr and PaO_2 <65 torr (FIO_2> .6). The PaO_2 increased from a mean of 51 torr without CPAP to 87 torr with CPAP. In 8 patients the increase in PaO_2 was adequate to permit continued CPAP while tracheal intubation was performed in the remaining 6. Changes in $PaCO_2$ were variable but in one patient hypoventilation ($PaCO_2$ 69 torr) was significant. Complications of CPAP include increased work of breathing, potential aspiration and discomfort from the tight mask fit. These data suggest CPAP can be effectively delivered without endotracheal intubation in selected patients. *(Greenbaum DM, Millen JE, Eross B et al: Continuous positive airway pressure without tracheal intubation in spontaneously breathing patients. Chest 69:615-620, 1976)*

Guest Reviewers

1976

Dr. J. Antonio Aldrete
Dr. Martha Anderson
Dr. Joseph P. Annis
Dr. James F. Arens
Dr. R. Dennis Bastron
Dr. George E. Battit
Dr. Donald W. Benson
Dr. James W. Bland
Dr. A. Jay Block
Dr. E. Walter Bowie
Dr. L. Donald Bridenbaugh
Dr. L. H. Brubaker
Dr. David L. Bruce
Dr. John M. R. Bruner
Dr. Stephen M. Brzica
Dr. Thomas Burns
Dr. Wilbur F. Cant
Dr. Robert T. Capps
Dr. Helmut F. Cascorbi
Dr. Francoise M. T. Carney
Dr. Harold Carron
Dr. Donald Caton
Dr. Ellis N. Cohen
Dr. Jack R. Collins
Dr. Julius H. Comroe
Dr. Thomas H. Corbett
Dr. Guenter Corssen
Dr. Mark B. Coventry
Mr. H. E. Cramp
Dr. Joseph Crehan
Dr. Roy F. Cucchiara
Dr. Jack Culligan
Dr. Francis J. Dannemiller
Dr. Michael J. Deegan
Dr. Ray Defalque
Dr. Ronald G. Dennis
Dr. Jay S. DeVore
Dr. Cosmo DiFazio
Dr. David Dines
Dr. W.H.L. Dornette
Dr. William Douglas
Dr. John B. Downs
Dr. Peter Dresel
Dr. Ronald Dueck
Dr. John W. Dundee
Dr. Michael Dykes
Dr. Douglas W. Eastwood
Dr. Edmond I. Eger, II
Dr. John H. Eisele
Dr. Frederick Ernst
Dr. G. W. Facer
Dr. William T. Foulk
Dr. Wesley T. Frazier
Dr. Bruce Friedman
Dr. Ghaleb Ghani
Dr. A. H. Giesecke
Dr. M. Frederica Godshalk
Dr. Alan Goldberg
Dr. John Gooding
Dr. Hymie Gordon
Dr. Allan B. Gould
Dr. Harold R. Griffith
Dr. Gerald A. Gronert
Dr. R. L. Hall
Dr. W. D. Hammond
Dr. John D. Harries
Dr. William M. Hart
Dr. Jan D. Hasbrouck
Dr. Kenneth Haselby
Dr. Terring W. Heironimus
Dr. David J. Hentges
Dr. Thomas Herrin
Mr. Benjamin Hippe
Dr. William S. Howland

Dr. William J. Johnson
Dr. Francis J. Kazmier
Dr. Elmer F. Klein, Jr.
Dr. Frank Knox
Dr. Gopal Krishna
Dr. Noel Lawson
Dr. Paul F. Leonard
Dr. Harry Lowe
Dr. Fred V. Lucas
Dr. Peere Lund
Dr. Albert Maduska
Dr. Richard I. Mazze
Dr. William McConahey
Dr. E. Scott McCord
Dr. Pearl McNall
Dr. Robert G. Merin
Dr. Joseph M. Messick, Jr.
Dr. James A. Meyer
Dr. Ronald D. Miller
Dr. Jerome H. Modell
Dr. Daniel C. Moore
Dr. S. S. Moorthy
Dr. Sheila Muldoon
Dr. Lee Nauss
Dr. Roger Neault
Dr. Gery O'Conner
Dr. P. J. Osmundsen
Dr. Richard Palahniuk
Dr. A. William Paulson
Dr. John I. Per-Lee
Dr. Lawrence Perry
Dr. Daniel Philbin
Dr. Otto C. Phillips
Dr. Charles B. Pittinger
Dr. Karen Price
Dr. Charles W. Quimby
Dr. Kai Rehder
Dr. Charles Restall
Dr. John C. Rieser
Dr. George Roffkar
Dr. Duane Rorie
Dr. William T. Ross
Dr. Randi Rosvoll
Dr. Edward E. Sammons
Dr. Robert R. Sawtell
Dr. Rick Schwettman
Dr. Gabriel F. Sciallis
Dr. Frank Sharbrough
Dr. Charles E. Short
Dr. Donald Silver
Dr. Carl A. Smith
Dr. Robert H. Smith
Dr. Robert M. Smith
Dr. John C. Snow
Dr. Wolfgang Spoerel
Dr. Michael d'Arcy Stanton-Hicks
Dr. Donald H. Stedman
Dr. David J. Steward
Dr. H. H. Stonnington
Dr. Y. F. Sung
Dr. Sait Tarhan
Dr. Howard Taswell
Dr. John H. Tinker
Dr. Daniel Traber
Dr. Charles Trey
Dr. W. A. Tweed
Dr. Patricia Underwood
Dr. Russell A. Van Dyke
Dr. Robert Virtue
Dr. John Wade
Dr. Leonard Walts
Dr. Josef Wang
Dr. Lyle Weed
Dr. Daniel Weidenthal
Dr. Roger D. White
Dr. Roger Wilson
Dr. Roy D. Wilson
Dr. Alon P. Winnie
Dr. Elémer Zsigmond

Books Received

Title	Author/Editor	Publisher	Pages	Price
Monographs in Anaesthesiology Volume 3: Muscle Relaxants	Ronald L. Katz (Editor)	New York American Elsevier Publishing Co. 1975	401	$49.95

This book provides basic information for the rational use of muscle relaxants.

The Anesthesiologist's Role in Pediatric Acute Care	Eric B. Furman (Editor)	Boston Little, Brown and Company 1975	231	

Problems of resuscitation, airway control, blood replacement and general supportive measures are more and more frequently becoming the responsibility of the anesthesiologist. This book provides basic knowledge for such acute care of children.

Physiological Basis of Anaesthesiology: Theory and Practice	W. W. Mushin J. S. Severinghaus M. Tiengo S. Gorini (Editors)	Padua, Italy Piccin Medical Books 1975	367	$20.00

This interesting and informative book is a compilation of material presented at the First International Seminar by internationally recognized participants.

Neurosurgical Anaesthesia 2nd Edition	A. R. Hunter	Philadelphia J. B. Lippincott Company 1975	344	$35.00

The first edition of this book was informative and useful. This second edition has required almost a total revision to bring it up-to-date.

Self Assessment in Anesthesiology	A. W. Grogono T. Hilary Howells	Chicago Year Book Medical Publishers, Inc. 1975	145	

This compilation of multiple-choice questions provides a useful adjunct for learning by the beginners as well as the more advanced student. Each question is supported by an answer.

Basic Physics in Anesthesiology: A Programmed Approach	L. Ivan Epstein Bernard A. Kuzava	Chicago Year Book Medical Publishers, Inc. 1976	388	

This book is written for the student with little or no prior knowledge of physics. Will be a useful source of information.

Clinical Use of Drugs in Renal Failure	Robert J. Anderson John G. Gambertoglio Robert W. Schrier	Springfield Charles C Thomas, Publisher 1975	251	$19.50

This book was written to assist physicians in taking care of patients with renal failure. The chapter on analgesic and soporific agents is important and useful.

Title	Author/Editor	Publisher	Pages	Price
Fundamentos de Anestesiologia 2a. edición	Guillermo Lopez Alonso	Mexico City La Prensa Medica Mexicana 1976	320	

Printed in Spanish, this book should be of real interest and value to our Spanish speaking colleagues.

Biotransformation of Local Anesthetics, Adjuvants, and Adjunct Agents	Gianfranco Dal Santo (Editor)	Boston Little, Brown and Company 1975	192	

Biotransformation and such related processes as distribution, elimination and protein binding of a number of agents are ably dealt with. Book warrants our attention.

Sleep 1974: Instinct, Neurophysiology, Endocrinology, Episodes, Dreams, Epilepsy and Intracranial Pathology	P. Bevin W. P. Poella (Editors)	New York S. Karger AG 1975	525	$76.50

This is a compilation of papers presented at the 2nd European Congress on Sleep Research held in Rome in 1974. To those interested in this particular subject, there are many hours of interesting reading.

Principles of Sedation, Local and General Anesthesia in Dentistry	Sylvan Myron Elliot Shane	Springfield Charles C Thomas, Publisher 1975	371	$19.00

The author, a dentist, has very ably drawn upon his own experience to write this text for dental anesthetists. Warrants reading.

Basic Problems in Burns	R. Vrabec Z. Konícková J. Moserová (Editors)	New York Avicenum, Czechoslovak Medical Press 1975	224	$25.00

This volume comprises the reports presented at the Symposium on the Treatment of Burns held in Prague September 1973. Several chapters are devoted to anesthesia and analgesia and resuscitation.

Local Anesthetics: Mechanisms of Action and Clinical Use	Benjamin G. Covino Helen G. Vassallo	New York Grune & Stratton 1976	173	$13.50

An interesting and informative little text on local anesthetic agents, starting with the discovery and use of cocaine brought up-to-date.

Tracheal Intubation	Edward L. Applebaum David L. Bruce	Philadelphia W. B. Saunders Company 1976	97	$9.50

This well-presented monograph, with very good illustrations and line drawings, will be interesting and useful for all medical and paramedical personnel involved in airway maintenance.

Anesthesia for the Uninterested	Alexander A. Birch John D. Tolmie	Baltimore University Park Press 1976	187	

A concise, frequently amusing, nicely illustrated, evening's reading.

Clinical Pharmacology in Dentistry	R. A. Cawson R. G. Spector	New York Churchill Livingstone 1975	254	$13.50

Dental practitioners must have a basic knowledge of pharmacology to use drugs to the advantage and benefit of their patients. This book concisely provides useful information.

	Author/Editor	Publisher	Pages	Price
1975 Year Book of Anesthesia	James E. Eckenhoff (Editor) David L. Bruce Edward A. Brunner H. Steele Holley Harry W. Linde (Associate Editors)	Chicago Year Book Medical Publishers, Inc. 1975	383	$18.50

Another informative addition to a series.

Anaesthesia for Eye, Ear, Nose and Throat Surgery	William F. K. Morrow James D. Morrison (Editors)	New York Churchill Livingstone 1975	149	

A small book containing much information. Will be particularly useful to students in training, but also will be helpful to more advanced consultants, both in our specialty and otorhinolaryngology.

Anaesthesie und Reanimation in der Kinderneurologie	Heinz Schoeppner Rosemarie A. Dietze Ursula Mielke	Leipzig VEB georg Thieme 1975	316	

An interesting and informative presentation of a subject about which most of us know too little.

Anesthesiology and the University	Nicholas M. Greene	Philadelphia J. B. Lippincott Company 1975	174	$10.00

An interesting and thought-provoking presentation by an outstanding author and anesthesiologist. Warrants your time for reading.

An Historical Account of Pharmacology: To the Twentieth Century	Chauncey D. Leake	Springfield Charles C. Thomas, Publisher 1975	210	$12.50

A very interesting personal historical dissertation on the development of our knowledge of drugs.

Current Topics in Critical Care Medicine	W. C. Shoemaker B. M. Travarese (Editors)	New York S. Karger, AG 1976	181	$36.00

This little paperback presents the proceedings of the Third International Symposium on Critical Care. Timely and useful information.

Intravenous Anaesthesia	John W. Dundee Gordon M. Wyant	Edinburgh Churchill Livingstone 1974	341	$28.50

An excellent comprehensive presentation of a special facet of our specialty. Much useful information.

Pediatric Anesthesia Case Studies	John G. Adams	Flushing, N.Y. Medical Examination Publishing Company, Inc. 1976	191	$10.00

Twenty-nine case histories followed by questions based on information furnished, plus the correct answers, with appropriate references. Readers may not agree with all the answers.

Title	Author/Editor	Publisher	Pages	Price
Self-Assessment of Current Knowledge in Anesthesiology	David L. Trickey	Flushing, N.Y. Medical Examination Publishing Company, Inc. 1976	180	$10.00

This volume comprises 1,142 multiple choice questions and answers referenced to current journal articles. An excellent guide for self-evaluation and continuing education.

Respiratory Therapy in Critical Care	Hugh S. Mathewson	Saint Louis The C. V. Mosby Company 1976	133	$6.50

Material in this little volume really is oriented toward the needs of the respiratory therapist. This book contains much useful information.

Development of Upper Respiratory Anatomy and Function: Implications for Sudden Infant Death Syndrome	James F. Bosma Jane Showacre (Editors)	Washington, DC US Government Printing Office 1976	279	$7.10

This book followed a symposium on Sudden Infant Death Syndrome. Thirty authors have contributed much information, well illustrated, with each chapter followed by appropriate references.

Evaluations of Drug Interactions Second Edition	—	Washington, DC American Pharmaceutical Association 1976	520	$12.50

Several thousand potential drug interactions are evaluated and discussed in this second edition, which is designed for every-day use by all health care practitioners. A significantly expanded index affords the quick access to information on specific interactions. Trade names are included in the index and are referenced to the appropriate nonproprietary term. This is a valuable source for authoritative, practical and complete drug interaction information.

Monographs in Anaesthesiology Vol. 5: Practical Regional Analgesia	J. Alfred Lee Robert Bryce-Smith (Editors)	New York Excerpta Medica 1976	232	$29.95

This book provides a guide to well-tried and commonly employed local and regional anesthetic technics.

The Human Larynx: A Functional Study	B. Raymond Fink	New York Raven Press 1975	193	

A nicely written, informative, well-illustrated book about an anatomic area about which most of us know too little.

Anesthesia for Open-Heart Surgery	Vieri Wiechman, MD (Editor)	Boston Little, Brown and Company 1976	277	

The physiological and clinical problems, as well as the practical management of different types of patients are ably addressed by authors from leading cardiac centres in Europe.

ANNUAL INDEX

VOLUME 55, 1976

Anesthesia AND Analgesia

.....CURRENT RESEARCHES

Official Journal of the International Anesthesia Research Society

A

A-aDo_2 after open-heart surgery 315-321

Aasheim GM: see Pflug AE jt auth

Abouleish E: Caudal analgesia for quadruplet delivery 61-66

Abouleish E: Postpartum hypertension and convulsion after oxytocic drugs 813-815

Abouleish E, Taylor FH: Effect of morphine-diazepam on signs of anesthesia, and dreams of patients under N_2O for cesarean section 702-705

Abramawitz MD: see Brodsky JB jt auth

Absorption-excretion volume effect, pulmonary 51-56

Acromegaly, laryngeal stenosis 57-60

Acupuncture anesthesia, a clinical study 508-512

Acupuncture, incidence of prolonged pain relief 229-234

Acute abdomen, unrelenting hypotension in a comatose hemophiliac child 346-349

Acute maxillary sinusitis complicating nasotracheal intubation, Brief Reports 885-886

Adams HJ, Blair MR Jr, Takman BH: The local anesthetic activity of tetrodotoxin alone and in combination with vasoconstrictors and local anesthetics 568-573

Adams HR, Mathew BP, Teske RH et al: Neuromuscular blocking effects of aminoglycoside antibiotics on fast-and-slow-contracting muscles of the cat 500-507

Adiposis dolorosa, management of intractable pain with intravenous lidocaine 257-259

Airway difficulties, laryngeal stenosis in acromegaly 57-60

Airway problem, tracheal bronchus, Brief Reports 746-747

Airway resistance, changes following droperidol, hydroxyzine, and diazepam 18-21

Albrecht RF: see Miletich DJ jt auth

Aldosterone, general anesthetic agents, and ouabain, effect on striated muscle contraction in toad 409-414

Aldrete JA: see Geevarghese KP jt auth

Aldrete JA, Tan ST, Carrow DJ et al: "Pentazepam" (pentazocine + diazepam) supplementing local analgesia for laparoscopic sterilization 177-181

Alexander JJ, Wall J: Righting the wrongs of writing: copy editors speak out, Editor's Choice 219-223

Alfonso AE: see Sklar GS jt auth

Allen GW: see Frederickson EL jt auth

Alveolar-arterial O_2 tension difference, factors affecting, open-heart surgery 315-321

Amaranath L, Andersen NB: The effect of general anesthetic agents, ouabain, and aldosterone on striated muscle contraction in toad 409-414

Amberg HL, Gordon G: Low-dose intramuscular ketamine for pediatric radiotherapy: a case report 92-94

Amberg HL: Use of monitor for ketamine in radiotherapy, Correspondence 895

Aminoglycoside antibiotics, neuromuscular blocking effects on the cat 500-507

Anaesthesia, history of ideas, Tenth Annual Becton, Dickinson and Company Oscar Schwidetzky Lecture 467-473

Analgesia, caudal for quadruplet delivery 61-66

epidural, bacteriologic aspects 187-190

local, supplemented by "pentazepam" for laparoscopic sterilization 177-181

methoxyflurane administration for vaginal delivery or cesarean section 415-419

narcotic versus post-thoracotomy intercostal block 542-546

Analgesic activity, butorphanol and morphine 394-401

Anaphylaxis, etiology and guidelines for management 493-499

Andersen NB: see Amaranath L jt auth

Andersen TW: see Lee PKY jt auth

Anderson EF: A potential ignition source in the operating room 217-218

Anderson N: see Ritter JG jt auth

Anesthesia, acupuncture, a clinical study 508-512

acute ethanol intoxication, effect on neonate, Brief Reports 602-603

analysis of tasks and human factors for coronary-artery bypass 374-377

anaphylaxis management 493-499

balanced, Questions and Answers 907-908

Bird® Mark-14 ventilator, Brief Reports 879

cardiac disease 617

circle systems, comparison of efficiency 724-729

clinical use of etomidate for induction 730-733

considerations for pericardectomy in uremic pericardial effusion 378-382

considerations in diffuse bleeding, diathesis of uncertain origin 173-176

cyclopropane, hypercapnia, Brief Reports 439-441

dissociative, ketamine, intraocular pressure 773-775

dissociative, ketamine tolerance 778-791

dosage nomogram for sodium nitroprusside induced hypotension 574-581

doxapram effects on cerebral blood flow and peripheral hemodynamics, goats 279-285

effect of general agents, ouabain, and aldosterone on striated muscle contraction in toad 409-414

electroanesthesia, monkey 536-541

endotracheal, laryngotracheal residue 392-393

enflurane and halothane, a comparative study using systolic time intervals 263-268

enflurane, cardiac decompensation, myotonia atrophica, Case History 433-436

enflurane, changes in blood chemistries 547-549

enflurane, COPD 806-809

enflurane, isoflurane, fluroxene, methoxyflurane and diethyl ether, effect on ouabain tolerance in the dog 360-365

estimation of solubility in blood, Brief Reports 593-595

gas machine hazards 26-33

general for blepharoplasty and rhytidectomy 165-167

general, neutrophil chemotaxis 668-673

general, recall 696-701

halothane and enflurane, absence of autoregulation of cerebral blood flow 100-109

halothane and succinylcholine, massive myoglobinuria 680-682

halothane MAC, effect of isoproterenol and propranolol in dogs 383-387

halothane MAC, phenobarbital in dogs 677-679

halothane, subsequent exposures in animals sensitized to a halothane metabolite, hepatic pathology 235-242

induction, etomidate 286-289

Anesthesia, (continued)
influence of pancuronium on potassium efflux produced by succinylcholine 474-477
isoflurane and halothane, hemodynamic effects, coronary artery disease 135-138
isoflurane, calibration of the Narkotest® gas monitor, Brief Reports 441-442
interaction of epinephrine with enflurane, isoflurane and halothane 709-712
intraoperative awakening for early recognition of possible neurologic sequelae during Harrington-rod spinal fusion 526-528
ketamine, arterial hypoxemia 311-314
laryngeal stenosis in acromegaly 57-60
legal aspects, physician-patient relationship, Questions and Answers 463-464
management in cardiac disease 622-625
modification of response to infection in mice 776-781
narcotic-supplemented, naloxone antagonism 800-805
nitrous oxide, absorption and excretion, pediatrics 95-99
nitrous oxide, effect of morphine-diazepam on awareness and dreams of patients for cesarean section 702-705
nitrous oxide, hepatic clearance of lidocaine in dogs 322-325
no liability for death of patient, Physician and the Law 759
obstetric, training centers in the U.S.A.—1975 839-845
patients early after infarction 640-642
patients with gas gangrene 247-252
patients with heart block and artificial cardiac pacemakers 626-632
preoperative evaluation and preparation of the cardiac 618-621
propranolol 1-5
rapid induction in combat casualties 74-76
regional, bupivacaine 763-768
regional, evaluation of memory 368-373
regional in renal transplantation 69-73
regional, lumbosacral plexus block 350-352
regional versus general, Questions and Answers 277-278
relation of $Paco_2$ to fresh gas flow in a circle system 706-708
respiratory distress with cardiovascular anomaly 481-484
severe hypertension, Wilms' tumor 519-521
simple method for inserting a nasogastric tube, Brief Reports 303-304
spinal, bupivacaine versus tetracaine
spinal, lumbar disc surgery 550-554
sodium nitroprusside-induced hypotension 654-662
theoretic significance of pH dependence of narcotics and narcotic antagonists 253-256
thiamylal-N_2O halothane, influence of pancuronium or d-tubocurarine circulatory responses 484-488
transcervical thymectomy 13-21
vanishing lung syndrome 750-752
Anesthesiologist, informed consent suit, Physician and the Law 906
no negligence in surgeon's failure to supervise, Physician and the Law 459
outpatient evaluation 307-310
Anesthetic, effect of oxygen 734-736
Anesthetic gas scavenger, Jackson-Rees system, Brief Reports 881-882
Anesthetic induction, circulatory changes 77-81
Anesthetic, inhalation, comparative study on pharmacokinetics and metabolism 853-862
Anesthetic, liability of manufacturer, Physician and the Law 202
Anesthetic, new intravenous—etoxadrol hydrochloride (CL-1848C; U-37862A) 335-339
Anesthetic, potency of lidocaine in the rat 818-821
Anesthetic wastes, effect on operating room personnel, Questions and Answers 760
Anesthetist, analysis of tasks and human factors for coronary-artery bypass 374-377
Animals, anesthesia and the modification of response to infection in mice 776-781
anesthetic potency of lidocaine in the rat 818-821
cardiovascular dynamics after large doses of fentanyl and nitrous oxide 168-172
cardiovascular effects of enflurane and halothane, Rhesus monkeys 85-91
effect of doxapram on cerebral blood flow and peripheral hemodynamics, goats 279-285
effect of enflurane, isoflurane, fluroxene, methoxyflurane and diethyl ether anesthesia on ouabain in the dog 360-365
effect of heparin on recovery from ischemic brain injuries in cats 683-687
effect of isoproterenol and propranolol on halothane MAC in dogs 383-387
electroanesthesia, Rhesus monkeys 536-541
halothane MAC, phenobarbital, dogs 677-679
hepatic clearance of lidocaine during nitrous oxide anesthesia in dogs 322-325
neuromuscular blocking effects of aminoglycoside antibiotics on the cat 500-507
preanesthetic evaluation and management of malignant hyperthermia, pigs 643-653
sensitization to a halothane metabolite and subsequent halothane exposure, hepatic pathology 235-242
Announcement: Nicholas M Greene, MD
Antagonism, naloxone 800-805
Antibiotics, aminoglycoside, neuromuscular blocking effects on the cat 500-507
muscle relaxants potentiated 224-228
prolonged epidural catheterization, Questions and Answers 132-133
Antihypertension, sodium nitroprusside 574-581
Anxiety, lorazepam premedication 792-796
Apnea, atypical pseudocholinesterase 243-246
prolonged, succinylcholine, Case History 737-739
Appendectomy, settlement for brain damage, Physician and the Law 45-46
Arterial hypoxemia, intravenous ketamine 311-314
Arterial oxygenation, decreased, sodium nitroprusside, Brief Reports 880-881
Artificial heart implantation, cardiovascular and respiratory effects of isoproterenol 560-567
ASA classification, Questions and Answers 614-615
Aspiration, tracheal 816-817
Atropine, pre-and post-anesthetic use in patients with glaucoma, Questions and Answers 460-461
Atypical pseudocholinesterase 243-246
Ausinsch B, Rayburn RL, Munson ES et al: Ketamine and intraocular pressure in children 773-775

Autoregulation, cerebral blood flow, halothane and enflurane anesthesia 100-109
Awareness and recall, perioperative 513-518
Awareness and dreams, effect of morphine-diazepam, nitrous oxide, cesarean section 702-705

B

Bacteriologic aspects, epidural analgesia 187-190
Bailey DR: see Kaplan JA jt auth
Balanced anesthesia, Questions and Answers 847-848
Bamforth BJ: see Celesia GG jt auth
Baraka A: A simple method of inserting a nasogastric tube for anesthesia, Brief Reports 303-304
Barash PG: see Meyers MB jt auth
Barash P, Kitahata LM, Mandel S: Acute cardiovascular collapse after intravenous phytonadione, Brief Reports 304-306
Barasch ST, Booth S, Modell JH: Hypercapnia during cyclopropane anesthesia: a case report, Brief Reports 439-441
Bartle S: see Eisele V jt auth
Bastron RD: $NaHCO_2$ use with the administration of bank blood, Questions and Answers 274-275
Battit GE: Regional versus general anesthesia, Questions and Answers 277-278
Bauer S: see Vaughan RW jt auth
Baxter-Travenol Lecturer (1977) Arthur C. Guyton, M.D. 891
Beck HA: see Pflug AE jt auth
Becton, Dickinson and Company Oscar Schwidetzky Memorial Lecturer (1977) William K. Hamilton, M.D. 890
Becton, Dickinson and Company Oscar Schwidetzky Memorial Lecture (1976) Vandam LD: On the history of ideas in anaesthesia 467-473
Bennett EJ: see Dalal FY jt auth
see Patel K jt auth
Benson DW, Kaufman JJ, Koski WS: Theoretic significance of pH dependence of narcotics and narcotic antagonists in clinical anesthesia 253-256
Bernhard W: see Cottrell JE jt auth
Bidwai AV: see Liu WS jt auth
Binda RE, Cook DR, Fischer CG: Advantages of infant ventilators over adapted adult ventilators in pediatrics 769-772
Bingham HG: see Modell JH jt auth
Birch AA, Boyce WH: Hypertension and decreased renal blood flow following methylene blue injection 674-676
Bird® Mark-14 anesthesia ventilator, Brief Reports 879
Blair MR Jr: see Adams HJ jt auth
Bleeding, diathesis of uncertain origin, anesthetic considerations 173-176
Blepharoplasty and rhytidectomy, general anesthesia 165-167
Blenkarn GD: Anesthetic considerations in patients with gas gangrene, Guest Discussion 252
Blitt CD, Petty WC, Wright WA et al: Clinical evaluation of injectable lorazepam as a premedicant: the effect on recall 522-525
Blitt CD: see Geha DC jt auth
Blockade, neuromuscular associated with trimethaphan 353-356
neuromuscular, circulatory responses and halothane concentrations during gastric or gallbladder traction 388-391
neuromuscular with pancuronium, acute renal failure 343-345
Block, caudal analgesia for quadruplet delivery 61-66
intercostal, post-thoracotomy 542-546
lumbosacral plexus, unusual complication 350-352
peripheral nerve, bupivacaine 763-768
stellate ganglion, effects on the idiopathic prolongation of the Q-T interval with cardiac arrhythmia 782-787
Blood, arterial and venous plasma levels of bupivacaine following peripheral nerve blocks 763-768
estimation of anesthetic solubility, Brief Reports 593-595
pH dependence of narcotics and narcotic antagonists 253-256
serum creatine phosphokinase, malignant hyperpyrexia 797-799
use of $NaHCO_3$ in administration of bank blood, Questions and Answers 274-275
Blood chemistries, enflurane anesthesia 547-549
Blood-gas exchange, effect of mechanical ventilation, end-inspiratory pause 122-130
Blood transfusion, cardiac failure associated with hypocalcemia 34-36
Blood volume determination, usefulness preoperatively, Questions and Answers 275-276
Body temperature maintenance by heated humidification 719-723
Bond VK: see Young SR jt auth
Booth S: see Barasch ST jt auth
Bough L: see Lear E jt auth
Boyan CP, Privitera PA: Resection of stenotic trachea: a case presentation 191-194
Boyce WH: see Birch AA jt auth
Brain damage, during appendectomy, Physician and the Law 45-46
Brain ischemic injuries, effect of heparin, cats 683-687
Breathalyzer test and exposure to anesthetic gases, Questions and Answers 615-616
Bridenbaugh LD: Regional versus general anesthesia, Questions and Answers 277-278
see Moore DC jt auth
Brief Reports
Fire hazard during CO_2 laser microsurgery on the larynx and trachea 146-147
A new introducer for percutaneous cardiovascular catheters 148-149
Plastic covered solid copper wire stylet 150
An unusual problem in nasotracheal extubation 302-303
A simple method of inserting a nasogastric tube for anesthesia 303-304
Acute cardiovascular collapse after intravenous phytonadione 304-306
Defective disposable endotracheal tube 437
Fatal complication from swallowed denture following prolonged endotracheal intubation 438-439
Hypercapnia during cyclopropane anesthesia 439-441
Calibration of the Narkotest® gas monitor for isoflurane 441-442
Prevention of hypothermia during cystoscopy in neonates 592-593
Estimation of anesthetic solubility in blood 593-595

Brief Reports, (continued)
Significance of Pco_2 within low-pressure endotracheal tube cuffs 595-596
Shearing hazard of intra-arterial Teflon catheters 597-598
Evaluation of larynx and trachea by xeroradiography 598-600
Pneumatocele of the larynx: a complication of percutaneous transtracheal ventilation 600-601
Acute ethanol intoxication and its prolonged effect on a full-term neonate 602-603
A precordial ECG lead for chest operations 740-741
A safety valve for the pediatric Rees system 741-743
Hazards of disposable rebreathing circuits 743-744
A PEEP device for a manual bag ventilator 745
The tracheal bronchus: an unusual airway problem 746-747
Innominate artery compression simulating cardiac arrest during mediastinoscopy: a case report 748-749
Anesthesia for vanishing lung syndrome: report of a case 750-752
Bronchial blockade in a child with a bronchopleural-cutaneous fistula using a balloon-tipped catheter 874-875
Difficult extubation of an endotracheal tube cuff 876-877
Humidity output of the Columbia pediatric system 877-879
Modification of a Bird® Mark-14 anesthesia ventilator for greater versatility 879
Decreased arterial oxygenation during sodium nitroprusside administration for intraoperative hypertension 880-881
An anesthetic gas scavenger for the Jackson-Rees system 881-882
A method for inserting the Carden tube 883-884
Acute maxillary sinusitis complicating nasotracheal intubation: a case report 885-886
Supine hypotensive syndrome caused by intra-abdominal mass: a case report 887-889
Brodsky JB, Abramawitz MD, Mehrez MP: Endobronchial intubation for intraoperative protection of a single functioning lung: a case report 340-342
Bronchial blockade, balloon-tipped catheter, Brief Reports 874-875
Bronchopleural-cutaneous fistula in a child, bronchial blockade, Brief Reports 874-875
Bronchus, tracheal, airway problem, Brief Reports 746-747
Brown EM: Intrathecal cold saline solution for intractable pain, Questions and Answers 131-132
Single-needle lateral approach for lumbar sympathetic block, Correspondence 451-453
Bruner JMR: Safety in operation of rechargeable ECG monitor (Tektronix®), Questions and Answers 613
Brunner EA: Absence of autoregulation of cerebral blood flow during halothane and enflurane anesthesia, Guest Discussion 106-107
see Fragen RJ jt auth
Buakham C: see Kim JM jt auth
Bupivacaine, arterial and venous plasma levels, peripheral nerve blocks 763-768
Bupivacaine versus tetracaine: spinal anesthesia 489-492
Burney RG, DiFazio CA: Hepatic clearance of lidocaine during N_2O anesthesia in dogs 322-325
Burney RG: see DiFazio CA jt auth
Butorphanol and morphine, parenteral analgesic activity 394-401

C

Calcaterra TC: see Carden E jt auth
Caldwell N: see Fragen RJ jt auth
Calverley RK: see Eger EI II jt auth
Campbell RL: see Gregg JM jt auth
Cant WF, Tinker JH, Tarhan S: Bronchial blockade in a child with a bronchopleural-cutaneous fistula using a balloon-tipped catheter, Brief Reports 874-875
Capps RT: ASA classification, Questions and Answers 614
Carbon dioxide laser microsurgery, larynx and trachea, fire hazard, Brief Reports 146-147
Carbon dioxide, level in circle system 706-708
Carden E, Calcaterra TC, Lechtman A: Pneumatocele of the larynx: a complication of percutaneous transtracheal ventilation, Brief Reports 600-601
Carden tube, method for inserting, Brief Reports 893-894
Cardiac arrhythmia, effects of stellate ganglion block on the idiopathic prolongation of the Q-T interval 782-787
Cardiac disease, anesthesia 617
Cardiac failure associated with hypocalcemia 34-36
Cardiac pacemakers, anesthesia 626-632
Cardiac surgery, cardiopulmonary bypass, effect of $Paco_2$ on O_2 consumption 269-273
cardiopulmonary bypass, protamine 110-113
factors affecting $A\text{-}aDo_2$ after open-heart surgery 315-321
hemodynamic effects of morphine 47-50
pericardectomy 378-382
Cardiac valve prosthesis, management of a parturient 214-216
Cardiology, anesthesia 617
anesthesia for patients early after infarction 640-642
anesthesia for patients with heart block and artificial cardiac pacemakers 626-632
anesthetic management 622-625
arrhythmia, effects of stellate ganglion block on the idiopathic prolongation of the Q-T interval 782-787
cardiac decompensation during enflurane anesthesia, myotonia atrophica, Case History 433-436
cardiac failure associated with hypocalcemia 34-36
cardiovascular effects of enflurane and halothane, Rhesus monkeys 85-91
circulatory changes during anesthetic induction 77-81
coronary artery disease, circulatory changes, following thiamylal-succinylcholine and tracheal intubation 232-234
drugs in supportive care 633-639
patients with pacemakers 626-632
precordial ECG lead, thoracotomy, Brief Reports 740-741
preoperative evaluation and preparation, patient with heart disease 618-621
management of a parturient with cardiac valve prosthesis 214-216
severe hypertension with Wilms' tumor 519-521

Cardiopulmonary bypass, effect of $Paco_2$ on O_2 consumption 269-273
protamine 110-113
Cardiovascular, comparative study of enflurane and halothane 263-268
coronary artery disease, hemodynamic effects of isoflurane and halothane 135-138
effects of cannabinol during oral surgery 203-213
effects of enflurane and halothane, Rhesus monkeys 85-91
Cardiovascular and respiratory effects of isoproterenol, artificial heart implantation 560-567
Cardiovascular dynamics, use of fentanyl and nitrous oxide in the dog 168-172
Cardiovascular surgery, analysis of tasks and human factors in anesthesia 378-382
respiratory distress with cardiovascular anomaly 481-484
Carrow DJ: see Aldrete JA jt auth
Carron H: Single-needle lateral approach for lumbar sympathetic block, Correspondence 451
Carter JD: see Venkateswarlu T jt auth
Caruso FS: see Tavakoli M jt auth
Cascorbi HF: see Hall RL jt auth
Case History: Gas embolism during encephalography 141-145
A life-threatening complication of cricothyroid membrane puncture 298-301
Cardiac decompensation during enflurane anesthesia in a patient with myotonia atrophica 433-436
Sustained high inspired Po_2 without toxic sequelae 588-591
Prolonged apnea after succinylcholine in a dental outpatient 737-739
Congenital lobar emphysema 869-873
Catheterization, epidural, antibiotics, Questions and Answers 132-133
Catheters, intra-arterial Teflon, shearing hazard, Brief Reports 597-598
Catheter, tracheobronchial suction 290-297
Cats, effects of heparin on recovery from ischemic brain injuries 683-687
neuromuscular blocking effects of aminoglycoside antibiotics on muscles 500-507
Caudal, analgesia, quadruplet delivery 61-66
Celesia GG, Bamforth BJ, Chen RC: Ketamine and epilepsy, Correspondence 445-446
Cerebral blood flow, effects of doxapram, goats 279-285
halothane and enflurane anesthesia 100-109
Cerebrospinal fluid pressure during oxygen encephalography, nitrous oxide inhalation 849-852
Cesarean section, effect of morphine-diazepam 702-705
renal function following methoxyflurane administration 415-419
Cestone KJ, Ryan WP, Loving CD: An anesthetic gas scavenger for the Jackson-Rees system, Brief Reports 881-882
Chalon J: see Ramanathan S jt auth
Chemistries, blood, enflurane 547-549
Chemotaxis, neutrophil, general anesthesia 668-673
Chen RC: see Celesia GG jt auth
Children, advantages of infant ventilators over adapted adult ventilators 769-772
bronchopleural-cutaneous fistula, bronchial blockade, Brief Reports 874-875
congenital lobar emphysema, Case History 869-873
ketamine and intraocular pressure 773-775
nitrous oxide anesthesia, absorption and excretion 95-99
nitrous oxide encephalography 402-408
radiotherapy, intramuscular ketamine 92-94
Romano-Ward syndrome, effects of stellate ganglion block on the idiopathic prolongation of the Q-T interval with cardiac arrhythmia 782-787
severe hypertension, Wilms' tumor 519-521
unrelenting hypotension associated with an acute abdomen in a comatose hemophiliac child 346-349
Chiu TM, Meyers EF: Defective disposable endotracheal tube, Brief Reports 437
Chronic obstructive pulmonary disease, enflurane anesthesia 806-809
Chu SS: Plasma concentration of lidocaine after endotracheal spray. Correspondence 117-118
Circulatory changes, anesthetic induction 77-81
Circulatory, changes in patients with coronary artery disease following thiamylal-succinylcholine and tracheal intubation 232-234
Circulatory responses during thiamylal-N_2O halothane anesthesia, influence of pancuronium or d-tubocurarine 485-488
Circulatory responses, halothane concentrations during gastric or gallbladder traction with and without neuromuscular blockade 388-391
Civetta JM: see Gallagher TJ jt auth
Clark RB: see Smith DB jt auth
Clinical investigation of a new intravenous anesthesia — etoxadrol hydrochloride (CL-1848C; U-37862A) 335-339
Cobb ML, Vaughan RW: Severe hypertension in a child with Wilms' tumor: a case report 519-521
Cocaine, current perspective 582-587
Cohen EN: Congenital abnormality in the children of exposed operating room personnel, Questions and Answers 760
Collins JR: Intrathecal cold saline solution for intractable pain, Questions and Answers 131-132
Columbia pediatric circle, humidity output, Brief Reports 877-879
Combat casualties, full stomachs, rapid induction 74-76
Communication, visual, clarity in lecture slides 6-12
Complications, acute ethanol intoxication, Brief Reports 602-603
acute maxillary sinusitis, nasotracheal intubation, Brief Reports 885-889
acute renal failure, pancuronium 343-345
acute respiratory failure 195-201
anaphylaxis management 493-499
anesthesia death, liability, Physician and the Law 759
anesthesia death, no negligence in surgeon's failure to supervise, Physician and the Law 459
anesthesia for patients early after infarction 640-642
anesthesia for patients with heart block and artificial cardiac pacemakers 626-632
anesthesia for transcervical thymectomy in myasthenia gravis 13-21
anesthesia in patients with gas gangrene 247-252
an unusual problem in nasotracheal extubation, Brief Reports 302-303

Complications, (continued)
arterial hypoxemia caused by intravenous ketamine 311-314
atypical pseudocholinesterase 243-246
brain damage during appendectomy, Physician and the Law 45-46
bronchopleural-cutaneous fistula, Brief Reports 874-875
cardiac decompensation during enflurane anesthesia, myotonia atrophica, Case History 433-436
cardiac failure associated with hypocalcemia 34-36
cardiovascular collapse following phytonadione, Brief Reports 304-306
catheter tip design, influence on tracheobronchial trauma and fluid aspirations efficiency 290-297
circulatory changes during anesthetic induction 77-81
congenital lobar emphysema, Case History 869-873
cricothyroid membrane puncture, Case History 299-301
decreased arterial oxygenation, sodium nitroprusside, Brief Reports 880-881
defective disposable endotracheal tube, Brief Reports 437
difficult extubation of an endotracheal tube cuff, Brief Reports 876-877
diffuse bleeding, diathesis of uncertain origin, anesthesia 173-176
drug interaction, muscle relaxants and antibiotics 224-228
effects of heparin on recovery from ischemic brain injuries, cats 683-687
fatality from swallowed denture following prolonged endotracheal intubation, Brief Reports 438
fire hazard, carbon dioxide laser microsurgery, larynx and trachea, Brief Reports 146-147
fluroxene toxicity 529-533
gas embolism, encephalography, Case History 141-145
hazards of disposable rebreathing circuits, Brief Reports 743-744
hypercapnia during cyclopropane anesthesia, Brief Reports 439-441
hypertension and decreased renal blood flow following methylene blue injection 674-676
hypertension, Wilms' tumor 519-525
hypotension, comatose hemophiliac child 346-349
hypothermia during cystoscopy in neonates, Brief Reports 592-593
innominate artery compression simulating cardiac arrest during mediastinoscopy 748-749
interaction of epinephrine with enflurane, isoflurane and halothane 709-712
intramuscular ketamine, pediatric radiotherapy 92-94
laryngeal stenosis in acromegaly 57-60
laryngotracheal residue during endotracheal anesthesia 392-393
lumbosacral plexus block 350-352
malignant hyperpyrexia, preplanned treatment 713-716
massive myglobinuria precipitated by halothane and succinylcholine 680-682
massive pulmonary hemorrhage complicating pulmonary embolectomy 182-184
methoxyflurane biotransformation and renal function 415-419
nitrous oxide encephalography, pediatrics 402-408
obesity, effect on postoperative oxygenation 37-41
parturient with cardiac valve prosthesis 214-216
pericardectomy, uremic pericardial effusion 378-382
perioperative awareness and recall 513-518
pneumatocele of the larynx, Brief Reports 600-601
postoperative hypoxemia 822-828
postpartum hypertension and convulsion after oxytocic drugs 813-815
prolonged apnea after succinylcholine, Case History 737-739
prolonged neuromuscular blockade 353-356
propranolol and surgical anesthesia 1-5
rapid induction, combat casualties 74-76
resection of stenotic trachea 191-194
respiratory distress with cardiovascular anomaly 481-484
shearing hazard of intra-arterial Teflon catheters, Brief Reports 597-598
significance of Pco_2, low pressure endotracheal tube cuffs, Brief Reports 595-596
supine hypotensive syndrome, intra-abdominal mass, Brief Reports 887-889
tracheal aspiration 816-817
tracheal bronchus, unusual airway problem, Brief Reports 746-747
treating acute heroin and methadone toxicity, Editor's Choice 607-610
vanishing lung syndrome, anesthesia 750-752
Congenital lobar emphysema, Case History 869-873
Congress 50th chronicle 428-431
50th program 151-163
50th report 420-427
Contamination, bacteriologic aspects of epidural analgesia 187-190
gas gangrene 247-252
Cook DR: see Binda RE jt auth
Cooke JE, Hood JB, Thomas JD: A method for inserting the Carden tube, Brief Reports 882-883
Corbett TH, Stedman DH: Breathalyzer test and exposure to anesthetic gases, Questions and Answers 615
Coronary-artery bypass, analysis of tasks and human factors in anesthesia 374-377
Coronary artery disease, circulatory changes following thiamylal-succinylcholine and tracheal intubation 232-234
hemodynamic effects of isoflurane and halothane 135-138
Corrections: First paragraph under discussion in the article "Comparison of Methotrimeprazine and Meperidine as Components of Balanced Anesthesia" which appeared in the Nov.-Dec. 1975 issue page 754, 46
Caption under photograph (bottom of page) May-June 1976 issue, page 424, 473
Correspondence: Fibrinogen and albumin deficiencies associated with packed red cell transfusions 114-115
Plasma concentration of lidocaine after endotracheal spray 116-118
Inadvertent epidural injection of thiopental 118-119
Awake endotracheal intubation 120
Intermittent mandatory ventilation 120-121

Correspondence, (continued)
Reversal of Datura stramonium delirium with physostigmine 260
Ketamine and epilepsy 445-451
Single-needle lateral approach for lumbar sympathetic block 451-454
Nonflammable germicides or detergents 606
Insect-sting kit 606
Plastic-covered wire stylet 755
Method to identify a cervical esophageal diverticulum during general anesthesia 893
Accuracy, brevity, clarity: three principles of good writing 893-895
Write to inform, not to impress 895
Use of monitor for ketamine in radiotherapy 895
What route of administration for K^+ solutions? 895-897
How do benefits of hemodilution balance O_2 reduction? 897-898
Effect of $Paco_2$ on O_2 consumption during cardiopulmonary bypass 898-899
Corssen G: see Gooding JM jt auth
see Tavakoli M jt auth
Cosmetic surgery, general anesthesia technic 165-167
Cottrell JE, Bernhard W, Turndorf H et al: Hazards of disposable rebreathing circuits, Brief Reports 743-744
Cottrell JE, Wolfson B, Siker ES: Changes in airway resistance following droperidol, hydroxyzine, and diazepam in normal volunteers 18-21
Cowan GSM: see Kano T jt auth
Cox BG: The author's editor, Editor's Choice 22-25
Craig DB: A life-threatening complication of cricothyroid membrane puncture, Case History Comment 299
Crawford AH, Jones CW, Perisho JA et al: Hypnosis for monitoring intraoperative spinal cord function 42-44
Creatine phosphokinase, malignant hyperpyrexia 797-799
Cricothyroid membrane puncture, Case History 299-301
Cromartie RS III: Rapid anesthesia induction in combat casualties with full stomachs 74-76
Crumrine RS: see Fraser JG jt auth
Cucchiara RF: A simple technic to minimize tracheal aspiration 816-817
see Isenhower N jt auth
see Mallow JE jt auth
Cuffs, endotracheal tubes, significance of Pco_2, Brief Reports 595-596
Cullen BF: see Duncan PG jt auth
Cumming JF: The development of an acute tolerance to ketamine 788-791
Cyclopropane anesthesia, hypercapnia, Brief Reports 439-441
Cystoscopy, neonates, prevention of hypothermia, Brief Reports 592-593

D

Dannemiller FJ: Epidural antibiotics with prolonged catheterization, Questions and Answers 132-133
see Douglas ME jt auth
Dalal FY, Bennett EJ, Grundy EM et al: Anesthetic considerations in diffuse bleeding diathesis of uncertain origin 173-176
Dalton B: A precordial ECG lead for chest operations, Brief Reports 740-741
Datta TD: see Ng TY jt auth
Defalque RJ: Single-needle lateral approach for lumbar sympathetic block, Correspondence 452-453
DelPizzo A: Nonflammable germicides or detergents, Correspondence 606
Denlinger JK, Nahrwold ML: Cardiac failure associated with hypocalcemia 34-36
Dennis RG: Gag reflex, Questions and Answers 461-462
Dentistry, cardiovascular effects of cannabinol during oral surgery 203-213
prolonged apnea after succinylcholine, Case History 737-739
Dercum's disease, management of intractable pain with intravenous lidocaine 257-259
Diazepam, droperidol, and hydroxyzine, changes in airway resistance 18-21
Diazepam-morphine, effect on awareness and dreams, nitrous oxide anesthesia, cesarean section 702-705
Diazepam + pentazocine supplementing local analgesia, laparoscopic sterilization 177-181
Dickson CM: see Silver DJ jt auth
Diethyl ether, effect of ouabain tolerance in the dog 360-365
DiFazio CA, Niederlehner JR, Burney RG: The anesthetic potency of lidocaine in the rat 818-821
see Burney RG jt auth
Digitalis tolerance, effect of enflurane, isoflurane, fluroxene, methoxyflurane and diethyl ether anesthesia in the dog 360-365
Digit-Symbol Test and Dot Test comparison for street fitness of outpatients 883-884
Disposable endotracheal tube, defective, Brief Reports 437
Disposable rebreathing circuits, Brief Reports 743-744
Dissociative anesthesia, intravenous ketamine, arterial hypoxemia 311-314
ketamine and intraocular pressure in children 773-775
ketamine tolerance 788-791
Dogs, cardiovascular dynamics after large doses of fentanyl and nitrous oxide 168-172
effect of enflurane, isoflurane, fluroxene, methoxyflurane and diethyl ether anesthesia on ouabain tolerance 360-365
effect of isoproterenol and propranolol on halothane MAC 383-387
halothane MAC, phenobarbital 677-679
hepatic clearance of lidocaine during nitrous oxide anesthesia 322-325
Dornette WHL: Physician-patient relationship, legal aspects of anesthesia, Questions and Answers 463
Dosage nomogram for sodium nitroprusside-induced hypotension under anesthesia 574-581
Doto JB: see Seltzer JL jt auth
Dot Test and Digit-Symbol Test comparison for street fitness of outpatients 883-884
Douglas ME, Downs JB, Dannemiller FJ et al: Change in pulmonary venous admixture with varying inspired oxygen 688-695
Downs JB: Effect of mechanical ventilation with end-inspiratory pause on blood-gas exchange, Guest Discussion 130
see Wright FG Jr jt auth

Downs ME: see Douglas ME jt auth

Down's syndrome, congenital lobar emphysema, Case History 869-873

Doxapram, effects on cerebral blood flow and peripheral hemodynamics, goats 279-285

Droperidol, hydroxyzine, and diazepam, changes in airway resistance 18-21

Drug addiction, cocaine, current perspective 582-587
treating acute heroin and methadone toxicity, Editor's Choice 607-610

Drug interaction, between d-tubocurarine, pancuronium, polymyxin B and neostigmine on neuromuscular function 224-228
epinephrine with enflurane, isoflurane and halothane in man 709-712

Drugs, cardiac supportive care 633-639

Drugs, Adrenalin® see epinephrine
aldosterone
Anectine® see succinylcholine
Antilirium® see physostigmine
AquaMephyton® see phytonadione
Arfonad® see trimethaphan
Ativan® see lorazepam
atropine
bupivacaine
butorphanol tartrate
cocaine
cyclopropane
Demerol® see meperidine
diazepam
diethyl ether
digitalis
Dopram® see doxapram
doxapram
droperidol
d-Tubocurarine
edrophonium
enflurane
epinephrine
ethanol
Ethrane® see enflurane
etomidate
etoxadrol hydrochloride (CL-1848C; U-37862A)
fentanyl
Fluoromar® see fluroxene
Fluothane® see halothane
fluroxene
Forane® see isoflurane
G Stophanthin® see ouabain
halothane
heparin
heroin
hydroxyzine
Inapsine® see droperidol
Inderal® see propranolol
isoflurane
isoproterenol
Isuprel® see isoproterenol
ketamine
Ketaject® see ketamine
Ketalar® see ketamine
lidocaine
lorazepam
Marcaine® see bupivacaine
meperidine
methadone
methoxyflurane
methylene blue
morphine
naloxone
Narcan® see naloxone
neostigmine
nitrous oxide
1-bromo-1,2,2-trifluorocyclobutane (42M-9)
ouabain
pancuronium
Pavulon® see pancuronium
pentazepam
pentazocine
Penthrane® see methoxyflurane
phenobarbital
physostigmine
phytonadione
polymyxin B
Pontocaine® see tetracaine
propranolol
Prostigmin® see neostigmine
protamine
sodium bicarbonate ($NaHCO_3$)
sodium nitroprusside
Sublimaze® see fentanyl
succinylcholine
Surital® see thiamylal
Tensilon Chloride® see edrophonium
tetracaine
$\triangle^9$tetrahydrocannabinol, THC
tetrodotoxin
thiamylal
trimethaphan
Tubarine® see d-Tubocurarine
tubocurarine see d-Tubocurarine
Valium® see diazepam
Xylocaine® see lidocaine

d-Tubocurarine, pancuronium, polymyxin B, and neostigmine, interaction on neuromuscular function 224-228

d-Tubocurarine pretreatment, circulatory changes during anesthetic induction 77-81

d-Tubocurarine or pancuronium influence on circulatory responses during thiamylal-N_2O halothane anesthesia 485-488

Dubovsky SL, Trustman R: Absence of recall after general anesthesia: implications for theory and practice 696-701

Dumke, Paul Rudolph: salutation to 443-444

Dunbar RW: see Kaplan JA jt auth
see Guffin AV jt auth

Dunbar RW: "Torr," origin of the word, Questions and Answers 131

Duncan PG, Cullen BF, Pearsall NN: Anesthesia and the modification of response to infection in mice 776-781

Dunsmore RH: see Silver DJ jt auth

E

Eastwood, Douglas W: salutation to 185-186

ECG rechargeable monitor (Tektronix®), Questions and Answers 613-614

Editing, relationship between author and editor, Editor's Choice 22-25
righting the wrongs of writing: copy editors speak out, Editor's Choice 219-223
Editor's Choice: The author's editor 22-25
Righting the wrongs of writing: copy editors speak out 219-223
Fundamental principles for preparing psychology journal articles 455-458
Treating acute heroin and methadone toxicity 607-610
Attorney urges study of doctors' professional relationships 756-758
Retrospectroscope . . . the soul of wit 900-905
Edrophonium antagonism and train-of-four-fade of neuromuscular block by succinylcholine in man 663-667
Eger, Edmond I II: salutation to 604-605
Eger EI II, Calverley RK, Smith NT: Changes in blood chemistries following prolonged enflurane anesthesia 547-549
see Harper M jt auth
see Johnston RR jt auth
see Tanifuji Y jt auth
Eibel P: Write to inform, not to impress, Correspondence 895
Eimerl D: see Perel A jt auth
Eisele V, Weinreich A, Bartle S: Perioperative awareness and recall 513-518
Eisenberg L: see Taub HA jt auth
Electroacupuncture, incidence of prolonged pain relief 229-234
Electroanesthesia, Rhesus monkeys 536-541
Electrocardiogram, precordial lead for chest operations, Brief Reports 740-741
El-Naggar M, Sadagopan S, Levine H: Factors influencing choice between tracheostomy and prolonged translaryngeal intubation in acute respiratory failure: a prospective study 195-201
Elwyn RA: cerebrospinal fluid pressure during O_2 encephalography and N_2O inhalation, Guest Discussion 851-852
Elwyn RA, Ring WH, Loeser E et al: Nitrous oxide encephalography: 5-year experience with 475 pediatric patients 402-408
Emphysema, congenital lobar, Case History 869-873
Encephalography, gas embolism, Case History 141-145
nitrous oxide, pediatrics 402-408
oxygen, with nitrous oxide inhalation, cerebrospinal fluid pressure 849-852
Endobronchial intubation for intraoperative protection of a single functioning lung 340-342
Endobronchial intubation, intraoperative protection, single functioning lung 340-342
Endotracheal anesthesia, laryngotracheal residue 392-393
Endotracheal intubation, prolonged, fatal complications from swallowed denture, Brief Reports 438
Endotracheal tube, Carden, Brief Reports 882-883
Endotracheal tube cuff, difficult extubation, Brief Reports 876-877
Endotracheal tube cuffs, significance of Pco_2, Brief Reports 595-596
Endotracheal tube, disposable, Brief Reports 437
Enflurane and halothane, absence of autoregulation of cerebral blood flow during anesthesia 100-109
cardiovascular effects on Rhesus monkey 85-91
comparative study using systolic time intervals 262-268
Enflurane anesthesia, cardiac decompensation, myotonia atrophica, Case History 433-436
Enflurane, anesthetic, COPD 806-809
changes in blood chemistries 547-549
effect of ouabain tolerance in the dog 360-365
Enflurane, isoflurane and halothane, comparative interaction of epinephrine in man 709-712
Epidemiology, bacteriologic aspects of epidural analgesia 187-190
Epidural analgesia, bacteriologic aspects 187-190
Epinephrine, enflurane, isoflurane and halothane, comparative interaction in man 709-712
Equipment, advantages of infant ventilators over adapted adult ventilators 769-772
anesthesia circle systems, comparison of efficiency 724-729
anesthetic gas scavenger, Jackson-Rees system, Brief Reports 881-882
balloon-tipped catheter use in bronchial blockade, Brief Reports 874-875
Bird® Mark-14 anesthesia ventilator, Brief Reports 879
calibration of the Narkotest® gas monitor for isoflurane, Brief Reports 441-442
Carden tube insertions, Brief Reports 882-883
Carlens tube 340-342
circle system, relation of $Paco_2$ to fresh gas flow 706-708
Columbia pediatric circle, Brief Reports 877-879
defective disposable endotracheal tube, Brief Reports 437
endotracheal tube, extubation difficulty, Brief Reports 876-877
gas machine hazards 26-33
hazards of disposable rebreathing circuits, Brief Reports 743-744
humidifier, maintenance of body temperature 719-723
immersion heater humidifiers 331-334
intra-arterial Teflon catheters, Brief Reports, 597-598
laser microsurgery, larynx and trachea, fire hazard, Brief Reports 146-147
low-pressure endotracheal tube cuffs, Brief Reports 595-596
mechanical ventilation, end-inspiratory pause, blood gas exchange 122-130
new percutaneous cardiovascular catheter introducer, Brief Reports 148-149
PEEP device for a manual bag ventilator, Brief Reports 745
plastic covered solid copper wire stylet, Brief Reports 150
precordial ECG lead, Brief Reports 740-741
preplanned for malignant hyperpyrexia 713-716
safety in operation of rechargeable ECG monitor (Tektronix®), Questions and Answers 613-614
safety valve for the pediatric Rees system, Brief Reports 741-743
tracheobronchial suction catheters 290-297
Erickson HH: see Ritzman JR jt auth
Ethanol intoxication, prolonged effect on a full-term neonate, Brief Reports 602-603
Etomidate, clinical use for anesthesia induction 730-733
ultrashort-acting nonbarbiturate agent for anesthesia induction 286-289

Etoxadrol hydrochloride (CL-1848C; U-37862A) new intravenous anesthetic 335-339

Extubation, difficulty, endotracheal tube cuff, Brief Reports 876-877

nasotracheal, unusual problem, Brief Reports 302-303

F

Familial nonprogressive muscular dystrophy, massive myglobinuria, halothane and succinylcholine anesthesia 680-682

Fanning GL: What route of administration for K^+ solutions?, Correspondence 895-897

Faust RJ, Nauss LA: Post-thoracotomy intercostal block: comparison of its effects on pulmonary function with those of intramuscular meperidine 542-546

Feingold A: Estimation of anesthetic solubility in blood, Brief Reports 593-595

see Kennedy PJ jt auth

see Velazquez JL jt auth

Use of monitor for ketamine in radiotherapy, Correspondence 895

Fentanyl and nitrous oxide, cardiovascular effects on dogs 168-172

Ferrer-Brechner T: Ketamine and epilepsy, Correspondence 446-447

Finck AJ: see Kripke BJ jt auth

Fink BR: Gag reflex, Questions and Answers 462-463

Fire hazard, carbon dioxide laser microsurgery, larynx and trachea, Brief Reports 146-147

Fire, potential ignition source in the operating room 217-218

Fischer CG: see Binda RE jt auth

Fiserova-Bergerova V: see Holaday DA jt auth

Flammable Hazards and Electrical Equipment, ASA Committee, operating room humidity, Questions and Answers 134

Fluid aspiration efficiency, influence of suction catheter tip design 290-297

Fluroxene, effect of ouabain tolerance in the dog 360-365

Fluroxene toxicity, chemical report 529-533

Fogdall RP: see VanNyhuis LS jt auth

Foley MF: see Wright FG Jr: jt auth

Forestner JE: Inadvertent epidural injection of thiopental, Correspondence 119

Fragen RJ, Caldwell N, Brunner EA: Clinical use of etomidate for anesthesia induction: a preliminary report 730-733

Fragen RJ, Caldwell N: Lorazepam premedication: lack of recall and relief of anxiety 792-796

Franken EA: see Moorthy SS jt auth

Fraser JG, Crumrine RS, Izant RJ Jr: A preplanned treatment for malignant hyperpyrexia 713-716

Frazier CA: Insect-sting kit, Correspondence 606

Frazier WT, Paulsen AW: Safety in operation of rechargeable ECG monitor (Tektronix®), Questions and Answers 613-614

Frederickson EL: Cardiovascular effects of enflurane and halothane on the Rhesus monkey, Guest Discussion 90-91

Frederickson EL, Longnecker DE, Allen GW: Clinical investigation of a new intravenous anesthetic — etoxadrol hydrochloride (CL-1848C; U-37862A) 335-339

Frederickson, Evan Lloyd: salutation to 67-68

Freeman JV: see Garcia-Bengochea F jt auth

Friedman BA: Fibrinogen and albumin deficiencies associated with packed red blood cell transfusions. Correspondence 114-115

Frost EAM: Outpatient evaluation: a new role for the anesthesiologist 307-310

Fuleihan SF, Wilson RS, Pontoppidan H: Effect of mechanical ventilation with end-inspiratory pause on blood-gas exchange 122-130

G

Gag reflex, Questions and Answers 461-463

Gallagher TJ, Civetta JM: Acute maxillary sinusitis complicating nasotracheal intubation: a case report, Brief Reports 885-886

Gallbladder traction, circulatory responses and halothane concentrations 388-391

Garcia-Bengochea F, Munson ES, Freeman JV: The lateral sitting position for neurosurgery 326-330

Gas embolism, encephalography, Case History 141-145

Gas evacuator, Jackson-Rees system, Brief Reports 881-882

Gas flow, circle system, relation of $Paco_2$ 706-708

Gas gangrene, anesthetic considerations 247-252

Gas machine, hazards 26-33

Gas monitor, Narkotest®, calibration, Brief Reports 441-442

Gastric traction, circulatory responses and halothane concentrations 388-391

Gastrointestinal surgery, circulatory responses and concentrations 388-391

Gay GR, Inaba DS, Rappolt RT Sr et al: "An' ho, ho, baby, take a whiff on me:" La Dama Blanca cocaine in current perspective 582-587

Gay GR, Inaba DS: Treating acute heroin and methadone toxicity, Editor's Choice 607-610

Geevarghese KP, Aldrete JA, Patel TC: Inspired air temperature with immersion heater humidifiers 331-334

Geha DG, Blitt CD, Moon BJ: Prolonged neuromuscular blockade with pancuronium in the presence of acute renal failure: a case report 343-345

General anesthesia, absence of recall 696-701

blepharoplasty and rhytidectomy 165-167

effect of anesthetic agents, ouabain, and aldosterone on striated muscle contraction, toad 409-414

neutrophil chemotaxis 668-673

General anesthesia versus regional, Questions and Answers 277-278

George RH: see James FM III jt auth

Gibbs PS, Moorthy SS, LoSasso AM: Sustained high inspired Po_2 without toxic sequelae, Case History 588-591

Gilbert, Richard George Barton, Salutation to 892

Gildea JE: see Lee CM jt auth

Girnar DS, Weinreich AI: Anesthesia for transcervical thymectomy in myastehnia gravis 13-21

Glaucoma, pre and post-anesthetic use of atropine, Questions and Answers 460-461

Goats, effect of doxapram on cerebral blood flow and peripheral hemodynamics 279-285

Goldberg AH: The patient with heart disease: preoperative evaluation and preparation 618-621

Gold MI: see Rodriguez R jt auth

Gooding JM, Corssen G: a new introducer for percutaneous cardiovascular catheters, Brief Reports 148-149

Etomidate: an ultrashort-acting nonbarbiturate agent for anesthesia induction 286-289

Gordon G: see Amberg HL jt auth
Gravenstein JS: Inadvertent epidural injection of thiopental, Correspondence 118-119
Green KW: Awake endotracheal intubation, Correspondence 120
Greene, Nicholas M: Announcement
Gregg JM, Campbell RL, Levin KJ et al: Cardiovascular effects of cannabinol during oral surgery 203-213
Gresham EL: Sustained high imspired Po_2 without toxic sequelae, Case History Discussion 590-591
Grossberg M: see Perel A jt auth
Grossman RK: see Ivankovich AD jt auth
Grundy EM: see Dalal FY jt auth
see Patel K jt auth
Guffin AV, Dunbar RW, Kaplan JA et al: Successful use of a reduced dose of protamine after cardiopulmonary bypass 110-113
Gynecology, laparoscopic sterilization, "pentazepam" supplementing local analgesia 177-181

H

Haid BC: see Kroesen GA jt auth
Hall JE: see Sudhir KG jt auth
Hall RL, Cascorbi HF: Breathalyzer test and exposure to anesthetic gases, Questions and Answers 615-616
Halothane and enflurane, absence of autoregulation of cerebral blood flow during anesthesia 100-109
cardiovascular effects on Rhesus monkeys 85-91
comparative study using systolic time intervals 263-268
Halothane and isoflurane, hemodynamic effects, coronary artery disease 135-138
Halothane and succinylcholine, massive myglobinuria 680-682
Halothane, concentrations during gastric or gallbladder traction, circulatory responses 388-391
Halothane, enflurane and isoflurane, comparative interaction of epinephrine in man 709-712
Halothane, MAC, in dogs, effect of isoproterenol and propranolol 383-387
Halothane, MAC, phenobarbital in dogs 677-679
Halothane metabolite and subsequent halothane exposures in animals, hepatic pathology 235-242
Halothane, subsequent exposures in animals sensitized to a halothane metabolite, hepatic pathology 235-242
Harlow HF: Fundamental principles for preparing psychology journal articles, Editor's Choice 455-458
Harper M, Eger EI II: A comparison of the efficiency of three anesthesia circle systems 724-729
Harrington procedure, intraoperative monitoring 42-44
Harrington-rod spinal fusion, intraoperative awakening for early recognition of possible neurologic sequelae 526-528
Harris PD: Medical Statistics, Statistical Pearls.
I. An empty shell game 82-84
II. How often did that happen? 357-359
III. The most likely interpretation 846-848
Harrison GG, Ivanetich K, Kaminsky L et al: Fluroxene (2,2,2-trifluroethyl vinyl ether) toxicity: a chemical aspect 529-533
Hassan SZ, Matz GJ, Lawrence AM et al: Laryngeal stenosis in acromegaly: a possible cause of airway difficulties associated with anesthesia 57-60
Hassan SZ: see Meltzer HY jt auth
Hazard, a potential ignition source in the operating room 217-218
disposable rebreathing circuits, Brief Reports 743-744
Heart, anesthesia for patients post infarction 640-642
Heart block, anesthesia 626-632
Heart disease, anesthetic management 622-625
preoperative evaluation and preparation 618-621
Heart implantation, artificial, cardiovascular and respiratory effects of isoproterenol 560-567
Heart transplant donor death, physician liability, Physician and the Law 611-612
Hematology, diffuse bleeding, diathesis of uncertain origin, anesthesia 173-176
unrelenting hypotension associated with an acute abdomen in a comatose hemophiliac child 346-349
Hemodynamics, cerebral and peripheral, effects of doxapram, goats 279-285
cerebral blood flow, halothane and enflurane anesthesia 100-109
estimation of anesthetic solubility in blood, Brief Reports 593-595
hypoxemia and hypocarbia following IPPB 555-559
isoflurane and halothane, coronary artery disease 135-138
morphine, cardiac surgery 47-50
pulmonary blood gas exchange, mechanical ventilation 122-130
pulmonary venous admixture changes with varying inspired oxygen 688-695
Hemophilia, unrelenting hypotension associated with an acute abdomen in a comatose hemophiliac child 346-349
Hemorrhage, pulmonary during pulmonary embolectomy 182-184
Heparin, effects on ischemic brain injuries, cats 683-687
Hepatic clearance of lidocaine during nitrous oxide in dogs 322-325
Hepatic dysfunction found by multiple laboratory screening 810-812
Hepatic, pathology in animals sensitized to a halothane metabolite and subsequent halothane exposures 235-242
Heroin and methadone toxicity, treatment, Editor's Choice 607-610
Hicks JS, Levinson G, Shnider SM: Obstetric anesthesia training centers in the U.S.A.—1975, 839-845
Hill GE: see Stanley TH jt auth
Hodgkinson R: see Kim SS jt auth
Holaday DA, Fiserova-Bergerova V: Uptake and excretion of 1-bromo-1,2,2-triflurocyclobutane (42M-9) in man: comparative study on pharmacokinetics and metabolism of inhalation anesthetics 853-862
Hood JB: see Cooke JE jt auth
Horn B: Single-needle lateral approach for lumbar sympathetic block, Correspondence 452
Howland WS: Fibrinogen and albumin deficiencies associated with packed red blood cell transfusions, Correspondence 115
$NaHCO_3$ use with the administration of bank blood, Questions and Answers 274-275
see Underwood P jt auth

Humidification, Columbia pediatric circle, Brief Reports 877-879
heated, maintenance of body temperature 710-723
Humidifiers, immersion heater, inspired air temperature 331-334
Humidity, operating rooms, Questions and Answers 134
Hydroxyzine, droperidol, and diazepam, changes in airway resistance 18-21
Hypercapnia during cyclopropane anesthesia, Brief Reports 439-441
Hypertension and convulsion postpartum after oxytocic drugs 813-815
Hypertension, decreased renal blood flow following methylene blue injection 674-676
intraoperative, sodium nitroprusside, Brief Reports 880-881
Wilms' tumor 519-521
Hyperthermia, malignant, massive myglobinuria, halothane and succinylcholine 680-682
malignant, preanesthetic evaluation and management, pig 643-653
Hypnosis, monitoring intraoperative spinal cord function 42-44
Hynotic, etomidate 286-289
Hypocalcemia, cardiac failure 34-36
Hypocarbia and hypoxemia following IPPB 555-559
Hypokalemia, management, Questions and Answers 276-277
Hypotension, induced with sodium nitroprusside 654-662
sodium nitroprusside, anesthesia 574-581
Hypotensive syndrome, intra-abdominal mass, Brief Reports 887-889
Hypothermia, prevention during cystoscopy in neonates, Brief Reports 592-593
Hypoxemia and hypocarbia following IPPB 555-559
Hypoxemia, intravenous ketamine 311-314
postoperative, early reversal 822-828

I

Inaba DS: see Gay GR jt auth
Induction, anesthetic, circulatory changes 77-81
anesthesia, etomidate 730-733
etomidate, an ultrashort-acting nonbarbiturate agent 286-289
rapid in combat casualties 74-76
Infants, prevention of hypothermia during cystoscopy, Brief Reports 592-593
prolonged effect of acute ethanol intoxication, Brief Reports 602-603
Infection, anesthesia, gas gangrene 247-252
modification of response and anesthesia in mice 776-781
Informed consent, suit against anesthesiologist, Physician and the Law 906
Inhalation anesthesia, comparative study on pharmacokinetics and metabolism 853-862
Innominate artery compression, simulating cardiac arrest during mediastinoscopy 748-749
Inspired air temperature with immersion heater humidifiers 331-334
Intercostal block, post-thoracotomy 542-546
Intermittent positive-pressure breathing, hypoxemia and hypocarbia 555-559
Intra-abdominal mass, supine hypotensive syndrome, Brief Reports 887-889
Intractable pain in adiposis dolorosa, management with intravenous lidocaine 257-259
Intractable pain, use of intrathecal cold saline, Questions and Answers 131-132
Intraocular pressure and ketamine in children 773-775
Intraoperative hypertension, sodium nitroprusside, Brief Reports 880-881
Intraoperative spinal cord function, monitoring using hypnosis 42-44
Introducer, for percutaneous cardiovascular catheters, Brief Reports 148-149
Intubation, endobronchial for intraoperative protection of a single functioning lung 340-342
endotracheal, prolonged, fatal complication from swallowed denture, Brief Reports 438
laryngeal stenosis in acromegaly 57-60
Intubation, nasotracheal, maxillary sinusitis, Brief Reports 885-886
rapid, combat casualties 74-76
tracheal and thiamylal-succinylcholine, circulatory changes in patients with coronary artery disease 232-234
translaryngeal, acute respiratory failure 195-201
IPPB, hypoxemia and hypocarbia 555-559
Ischemic brain injuries, effect of heparin, cats 683-687
Isenhower N, Cucchiara RF: Anesthesia for vanishing lung syndrome: report of a case 750-752
Isern-Amaral J: see Liu WS jt auth
Isoflurane and halothane, hemodynamic effects, coronary artery disease 135-138
Isoflurane anesthesia, calibration of the Narkotest® gas monitor, Brief Reports 441-442
Isoflurane, effect of ouabain tolerance in the dog 360-365
Isoflurane, enflurane and halothane, comparative interaction of epinephrine in man 709-712
Isoproterenol and propranolol, effect on halothane MAC in dogs 383-387
Isoproterenol, cardiovascular and respiratory effects, artificial heart implantation 560-567
Ivanetich K: see Harrison GG jt auth
Ivankovich AD: Absence of autoregulation of cerebral blood flow during halothane and enflurane anesthesia, Reply to Dr. Brunner's comments 107-109
Ivankovich AD, Miletich DJ, Grossman RK et al: The effect of enflurane, isoflurane, fluroxene, methoxyflurane and diethyl ether anesthesia on ouabain tolerance in the dog 360-365
Ivankovich AD: see Miletich DJ jt auth
Iwane T, Maruyama M, Matsuki M et al: Management of intractable pain in adiposis dolorosa with intravenous administration of lidocaine 257-259
Izant RJ Jr: see Fraser JG jt auth

J

Jackson-Rees system, anesthetic gas scavenger, Brief Reports 881-882
Jacoby J: see Seltzer JL jt auth
Jadwat C: see Lear E jt auth
James FM III, George RH, Naiem H et al: Bacteriologic aspects of epidural analgesia 187-190
Janis KM: Intermittent mandatory ventilation, Correspondence 120-121

Johnston RR, Eger EI II, Wilson C: A comparative interaction of epinephrine with enflurane, isoflurane and halothane in man 709-712

Joint Commission on Hospital Accreditation, operating room humidity, Questions and Answers 134

Jones CS: Modification of a Bird® Mark-14 ventilator for greater versatility, Brief Reports 879

Jones CW: see Crawford AH jt auth

Jordan WS: Ketamine and epilepsy, Correspondence 447-449

Journalism, fundamental principles for preparing psychology journal articles, Editor's Choice 445-458

the author's editor, Editor's Choice 22-25

righting the wrongs of writing: copy editors speak out, Editor's Choice 219-223

K

Kaminsky L: see Harrison GG jt auth

Kano T, Cowan GSM, Smith RH: Electroanesthesia (EA) studies: EA produced by stimulation of sensory nerves of the scalp in Rhesus monkeys 536-541

Kaplan JA, Dunbar RW: Propranolol and surgical anesthesia 1-5

Kaplan JA, Miller ED, Bailey DR: A comparative study of enflurane and halothane using systolic time intervals 263-268

Kaplan JA: see Guffin AV jt auth

Katz H, Machida RC, Wootton DG et al: A technic of general anesthesia for blepharoplasty and rhytidectomy 165-167

Kaufman JJ: see Benson DW jt auth

Kemi C: see Yanagida H jt auth

Kennedy PJ, Feingold A, Wiener EL et al: Analysis of tasks and human factors in anesthesia for coronary-artery bypass 374-377

Ketamine and intraocular pressure in children 773-775

Ketamine, arterial hypoxemia 311-314

pediatric radiotherapy 92-94

Ketamine tolerance 788-791

Kidney, acute failure, pancuronium 343-345

transplantation, regional anesthesia 69-73

Kim JM, Buakham C, McAmis F: Supine hypotensive syndrome caused by intra-abdominal mass: a case report, Brief Reports 887-889

Kim SS, Hodgkinson R: Acute ethanol intoxication and its prolonged effect on a full-term neonate, Brief Reports 602-603

King BD: see Sklar GS jt auth

King H: see Moorthy SS jt auth

King J: Prolonged apnea after succinylcholine in a dental outpatient, Case History, Guest Discussion 738-739

Kitahata LM: see Barash P jt auth

Konchigeri HN, Levitsky S: Anesthetic considerations for pericardectomy in uremic pericardial effusion 378-382

Konchigeri HN, Tay CH: Influence of pancuronium on potassium efflux produced by succinylcholine 474-477

Kopman AF: Effect of $Paco_2$ on O_2 consumption during cardiopulmonary bypass, Correspondence 888

How do benefits of hemodilution balance O_2 reduction?, Correspondence 887

Koski WS: see Benson DW jt auth

Kothary SP: see Zsigmond EK jt auth

Kripke BJ, Finck AJ, Shah NK et al: Naloxone antagonism after narcotic-supplemented anesthesia 800-805

Kroesen GA, Haid BC: Fatal complication from swallowed denture following prolonged endotracheal intubation: a case report, Brief Reports 438

Kushins LG: see Wollman SB jt auth

L

Laboratory screening, unexpected hepatic dysfunction 810-812

Laflin MJ, Tobey RE, Reves JG: Anesthetic considerations in patients with gas gangrene 247-252

Laparoscopic sterilization, "pentazepam" supplementing local analgesia 177-181

Laryngeal stenosis, acromegaly 57-60

Laryngotracheal residue, endotracheal anesthesia 392-393

Larynx and trachea, evaluation by xeroradiography, Brief Reports 598-600

Larynx, pneumatocele, a complication of percutaneous transtracheal ventilation, Brief Reports 600-601

Laser microsurgery, carbon dioxide, larynx and trachea, fire hazard, Brief Reports 146-147

Lateral sitting position for neurosurgery 326-330

Laver MB: Management of patient with hypokalemia on diuretic therapy, Questions and Answers 276-277

What route of administration for K^+ solutions?, Correspondence 895-896

Lawrence AM: see Hassan SZ jt auth

Lawson NW, Thompson DS, Nelson CL et al: A dosage nomogram for sodium nitroprusside-induced hypotension under anesthesia 574-581

Lawson NW, Thompson DS, Nelson CL et al: Sodium nitroprusside-induced hypotension for supine total hip replacement 654-662

Lear E, Jadwat C, Bough L et al: Atypical pseudocholinesterase: a clinical report 243-246

Lechtman A: see Carden E jt auth

Lecture slides, visual communication 6-12

Lee CM, Gildea JE: Laryngotracheal residue during endotracheal anesthesia 392-393

Lee C: Train-of-four-fade and edrophonium antagonism of neuromuscular block by succinylcholine in man 663-667

Lee JH, Salvatore A: Innominate artery compression stimulating cardiac arrest during mediastinoscopy: a case report 748-749

Lee PKY, Modell JH, Andersen TW et al: Incidence of prolonged pain relief following acupuncture 229-234

Lee PKY: see Modell JH jt auth

Legal aspects of anesthesia, physician-patient relationship, Questions and Answers 463-464

Leonard PF: Nonflammable germicides or detergents, Correspondence 606

Levesque PR: Significance of Pco_2 within low-pressure endotracheal tube cuffs, Brief Reports 595-596

Levine H: see El-Naggar jt auth

Levin KJ: see Gregg JM jt auth

Levinson G: see Hicks JS jt auth

Levitsky S: see Konchigeri HN jt auth

Liability, death of heart transplant donor, Physician and the Law 611-612
Liability of manufacturer, Physician and the Law 202
Lidocaine, anesthetic potency in the rat 818-821
management of intractable pain in adiposis dolorosa 257-259
nitrous oxide anesthesia, hepatic clearance in dogs 322-325
Lindop AE: see Pflug AE jt auth
Linke CL, Merin RG: A regional anesthetic approach for renal transplantation 69-73
Link WJ, Spaeth EE, Wahle WM et al: The influence of suction catheter tip design on tracheobronchial trauma and fluid aspiration efficiency 290-297
Liu WS, Bidwai AV, Stanley TH et al: Cardiovascular dynamics after large doses of fentanyl and fentanyl plus nitrous oxide in the dog 168-172
Liu WS, Stanley TH, Isern-Amaral J et al: Cardiovascular and repiratory effects of isoproterenol before and after artificial heart implantation 560-567
Liver, dysfunction found by multiple laboratory screening 810-812
hepatic clearance of lidocaine during nitrous oxide anesthesia in dogs 322-325
pathology in animals sensitized to a halothane metabolite and subsequent halothane exposures 235-242
Local analgesia, supplemented by "pentazepam" for laparoscopic sterilization 177-181
Local anesthetic action of tetrodotoxin 568-573
Local anesthetics, obstetrics 829-838
Loeser E: see Elwyn RA jt auth
Longnecker DE: see Frederickson EL jt auth
Lorazepam as a premedicant, evaluation of memory under regional anesthesia 368-373
Lorazepam, clinical evaluation as a premedicant, the effect on recall 522-525
Lorazepam premedication: lack of recall and relief of anxiety 792-796
LoSasso AM: see Gibbs PS jt auth
see Moorthy SS jt auth
Loving CD: see Cestone KJ jt auth
Lumbar disc surgery, spinal anesthesia 550-554
Lumbosacral plexus block, unusual complication 350-352
Lungs, absorption-excretion volume effect 51-56
Lung, single functioning, endobronchial intubation for intraoperative protection 340-342
Luther RR: see Morrow DH jt auth

M

MAC, halothane, effect of isoproterenol and propranolol on dogs 383-387
Machida RC: see Katz H jt auth
Madura JA: see Stoelting RK jt auth
Malignant hyperpyrexia, isoenzymes of creatine phosphokinase in serum 797-799
preplanned treatment
Malignant hyperthermia, massive myglobinuria, halothane and succinylcholine 680-682
preanesthetic evaluation and management in the pig 643-653
Mallow JE, White RD, Cucchiara RF et al: Hemodynamic effects of isoflurane and halothane in patients with coronary artery disease 135-138
Malpractice, attorney urges study of doctors' professional relationships, Editor's Choice 756-758
Mandel S: see Barash P jt auth
Maniscalco JE: see Paul WL jt auth
Mark-14, Bird® ventilator 879
Martin JT: Congenital lobar emphysema, Case History 869-873
Maruyama M: see Iwane T jt auth
Marx GF: see Saka DM jt auth
Mather LE: see Moore DC jt auth
Mathew BP: see Adams HR jt auth
Matsuki A: see Zsigmond EK jt auth
Matsuki M: see Iwane T jt auth
Matz GJ: see Hassan SZ jt auth
Maxillary sinusitis, nasotracheal intubation, Brief Reports 885-886
McAlpine FS: see Nicholson MJ jt auth
McAmis F: see Kim JM jt auth
McComb SJ: Visual communication: clarity in lecture slides revisited 6-12
McCord ES: Change in pulmonary venous admixture with varying inspired oxygen, Guest Discussion 693-695
McCracken LE Jr: see Reves JG jt auth
McGrath CJ: see Short CE jt auth
McLaren RG, Moffitt EA: Prolonged apnea after succinylcholine in a dental outpatient, Case History 737-739
McQueen MJ: Prolonged apnea after succinylcholine in a dental outpatient, Case History, Guest Discussion 738-739
Mechanical ventilation, end-inspiratory pause, blood-gas exchange 122-130
Mediastinoscopy, innominate artery compression simulating cardiac arrest 748-749
Medical Statistics: Statistical Pearls
I. An empty shell game 82-84
II. How often did that happen? 357-359
III. The most likely interpretation 846-848
Medico-legal (Physician and the Law)
$1,237,500 settlement for brain damage during appendectomy 45-46
Anesthetic manufacturer not liable for death of patient 202
No negligence in surgeon's failure to supervise anesthesiologist 459
Physician liability for death of heart transplant donor discussed 611-612
No liability for death of patient during anesthesia 759
Informed consent suit against anesthesiologist 906
Attorney urges study of doctors' professional relationships, Editor's Choice 756
Mehrez MP: see Brodsky JB jt auth
Meltzer HY, Hassan SZ, Russo P et al: Isoenzymes of creatine phosphokinase in serum of families with malignant hyperpyrexia 797-799
Memory, absence of recall, general anesthesia 696-701
lorazepam premedication 792-796
Memory under regional anesthesia, intravenous lorazepam as a premedicant 368-373
Mendelson G: Reversal of Datura stramonium with physostigmine, Correspondence 260
Meperidine, comparison of effects on pulmonary function with post-thoracotomy intercostal block 542-546

Merin RG: see Linke CL jt auth
Terminology and definition of word "metabolism," Questions and Answers 760-761
Metabolism, definition, Questions and Answers 760-761
Methadone and heroin toxicity, treatment, Editor's Choice 607-610
Methoxyflurane biotransformation and renal function, vaginal delivery or cesarean section 415-419
Methoxyflurane, effect of ouabain tolerance in the dog 360-365
Methylene blue, hypertension and decreased renal blood flow 674-676
Meyer JA: Humidity in operating rooms, Questions and Answers 134
Meyers EF: see Chiu TM jt auth
Meyers MB, Barash PG: Cardiac decompensation during enflurane anesthesia in a patient with myotonia atrophica, Case History 433-436
Meyers MB, Oh TH: Prevention of hypothermia during cystoscopy in neonates, Brief Reports 592-593
Mice, anesthesia and the modification of response to infection 776-781
Microsurgery, carbon dioxide laser, larynx and trachea, Brief Reports 146-147
Miletich DJ, Ivankovich AD, Albrecht RF et al: Absence of autoregulation of cerebral blood flow during halothane and enflurane anesthesia 100-109
The effects of doxapram on cerebral blood flow and peripheral hemodynamics in the anesthetized and unanesthetized goat 279-285
Miletich DJ: see Ivankovich AD jt auth
Miller ED: see Kaplan JA jt auth
see Ritzman JR jt auth
Miller RD: see Van Nyhuis LS jt auth
see Wilson SL jt auth
Miller R: see Tausk HC jt auth
Modell JH, Lee PKY, Bingham HG et al: "Acupuncture anesthesia"—a clinical study 508-512
Modell JH: see Barasch ST jt auth
see Lee PKY jt auth
Moffitt EA: Anesthesia for patients early after infarction 640-642
Anesthesia for the patient with cardiac disease: preamble 617
Prolonged apnea after succinylcholine in a dental outpatient, Case History Comment 738
see McLaren RG jt auth
Moffitt EA, Tarhan S, Rodriguez R et al: Hemodynamic effects of morphine during and early after cardiac operations 47-50
Monitoring, intraoperative spinal cord function using hypnosis 42-44
Monkey, electroanesthesia 536-541
Rhesus, cardiovascular effects on enflurane and halothane 85-91
Moon BJ: see Geha DG jt auth
Moore DC, Mather LE, Bridenbaugh LD et al: Arterial and venous plasma levels of bupivacaine following peripheral nerve blocks 763-768
Moore EB: Attorney urges study of doctors' professional relationships, Editor's Choice 756-758
Moore WE, Watson RL, Summary JJ: Massive myglobinuria precipitated by halothane and succinylcholine in a member of a family with elevation of serum creatine phosphokinase 680-682
Moorthy SS, Franken EA, LoSasso AM et al: Respiratory distress with left aortic arch, right descending aorta, and right ligamentum arteriosum: a case report 481-484
Moorthy SS, LoSasso AM, King H et al: Evaluation of larynx and trachea by xeroradiography, Brief Reports 598-600
Moorthy SS: see Gibbs PS jt auth
Morphine and butorphanol, parenteral analgesic activity 394-401
Morphine-diazepam, effect on awareness and dreams, nitrous oxide anesthesia, cesarean section 702-705
Morphine, hemodynamic effects, cardiac surgery 47-50
Morrow DH: Cardiac decompensation during enflurane anesthesia in a patient with myotonia atrophica, Case History Comment 436
Morrow DH, Luther RR: Anaphylaxis: etiology and guidelines for management 493-499
Muldoon SM: Preoperative blood volume determination, Questions and Answers 275-276
Munson ES: Cardiac decompensation during enflurane anesthesia in a patient with myotonia atrophica, Case History Comment 435
see Ausinsch B jt auth
see Garcia-Bengochea F jt auth
see Paul WL jt auth
Muravchick S, Owens WD: An unusual complication of lumbosacral plexus block: a case report 350-352
Murphy TM: see Pflug AE jt auth
Muscle relaxants, atypical pseudocholinesterase 243-246
effects on circulatory response 485-488
influence on potassium efflux 474-477
interaction with antibiotics 224-228
train-of-four fade, edrophonium antagonism, 663-667
Myasthenia gravis, anesthesia, transcervical thymectomy 13-21
Myocardial infarction, anesthesia 640-642
Myotonia atrophica, cardiac decompensation, enflurane anesthesia, Case History 433-436

N

Nahrwold ML: see Denlinger JK jt auth
Naiem H: see James FM III jt auth
Naloxone, antagonism after narcotic-supplemented anesthesia 800-805
Narcotic analgesia versus post-thoracotomy intercostal block 542-546
Narcotic antagonists and narcotics, pH dependence in clinical anesthesia 253-256
Narcotic, cocaine, current perspective 582-587
morphine hemodynamic effects, cardiac surgery 47-50
Narcotics and narcotic antagonists, pH dependence in clinical anesthesia 253-256
Narcotics, morphine and butorphanol, double-blind comparison of their parenteral analgesic activity 394-401
morphine-diazepam, awareness and dreams, nitrous oxide anesthesia, cesarean section 702-705
Narcotic-supplemented anesthesia, naloxone antagonism 800-805
Narcotics, treating acute heroin and methadone toxicity, Editor's Choice 607-610

Narkotest® gas monitor, calibration, Brief Reports 441-442

Nasogastric tube, a simple method of insertions, Brief Reports 303-304

Nasotracheal extubation, unusual problem, Brief Reports 302-303

Nasotracheal intubation, acute maxillary sinusitis, Brief Reports 885-889

National Fire Protection Association, potential ignition source 217-218

Nauss LA: see Faust RJ jt auth

Negligence, not found in surgeon's failure to supervise anesthesiologist, Physician and the Law 459

Nelson OL: see Lawson NW jt auth

Neonatal, obstetric anesthesia training centers in the U.S.A.—1975, 839-845

Neonate, prolonged effect of acute ethanol intoxication, Brief Reports 602-603

Neonates, prevention of hypothermia during cystoscopy, Brief Reports 592-593

Neostigmine, d-tubocurarine, pancuronium and polymyxin B, interaction on neuromuscular function 224-228

Nephrology, acute renal failure, prolonged neuromuscular blockade with pancuronium 343-345

renal transplantation, regional anesthesia 69-73

severe hypertension, Wilms' tumor 519-521

Nerve blocks, peripheral, arterial and venous plasma levels of bupivacaine 763-768

Nerve stimulation, electroanesthesia, monkey 536-541

Neuromuscular blockade associated with trimethaphan 353-356

Neuromuscular blockade, circulatory responses and halothane concentrations during gastric or gallbladder traction 388-391

prolonged, with pancuronium, acute renal failure 343-345

Neuromuscular block by succinylcholine, train-of-four fade and edrophonium antagonism 663-667

Neuromuscular blocking effects of aminoglycoside antibiotics on cat 500-507

Neuromuscular function, interaction between d-tubocurarine, pancuronium, polymyxin B, and neostigmine 224-228

Neurologic sequelae, intraoperative awakening for possible early recognition, Harrington-rod spinal fusion 526-528

Neurology, familial nonprogressive muscular dystrophy, massive myoglobinuria precipitated by halothane and succinylcholine 680-682

ischemic brain injuries, effects of heparin, cats 683-687

myasthenia gravis, transcervical thymectomy 13-21

myotonia atrophica, cardiac decompensation during enflurane anesthesia, Case History 433-436

Neurosurgery, cerebrospinal fluid pressure, oxygen encephalography 849-852

encephalography, gas embolism, Case History 141-145

lateral sitting position 326-330

neuromuscular blockade associated with trimethaphan 353-356

nitrous oxide encephalography, pediatrics 402-408

Neutrophil chemotaxis, general anesthesia 668-673

NFPA Standards, operating room humidity, Questions and Answers 134

Ng TY, Datta TD: Difficult extubation of an endotracheal tube cuff, Brief Reports 876-877

Nicholson MJ: Plastic-covered solid copper wire stylet, Brief Reports 150

Plastic-covered wire stylet, Correspondence 755

Nicholson MJ, McAlpine FS: Method to identify a cervical esophageal diverticulum during general anesthesia, Correspondence 893

Niederlehner JR: see DiFazio CA jt auth

Nitrous oxide absorption, endotracheal tube cuffs, Brief Reports 595-596

Nitrous oxide anesthesia, effect of morphine-diazepam on awareness and dreams of patients for cesarean section 702-705

hepatic clearance of lidocaine in dogs 322-325

Nitrous oxide encephalography, pediatrics 402-408

Nitrous oxide inhalation and oxygen encephalography, cerebrospinal fluid pressure 849-852

Nitrous oxide volumes, absorbed and excreted, pediatric anesthesia 95-99

Norton ML: see Snow JC jt auth

O

Obesity, effect of position on postoperative oxygenation 37-41

Obstetrics, acute ethanol intoxication, prolonged effect on neonate, Brief Reports 602-603

anesthesia training centers in the U.S.A.—1975, 839-845

caudal analgesia for quadruplet delivery 61-66

effect of morphine-diazepam on awareness and dreams of patients under nitrous oxide anesthesia for cesarean section 702-705

local anesthetics 829-838

management of a parturient with cardiac valve prosthesis 214-216

physostigmine reversal of sedation in parturients 478-480

postpartum hypertension and convulsion after oxytocic drugs 813-815

renal function following methoxyflurane administration 415-419

Oh TH: see Meyers MB jt auth

Okuda Y: see Sari A jt auth

Oncology, radiotherapy, pediatrics, intramuscular ketamine 92-94

1-bromo-1,2,2-trifluorocyclobutane (42M-9), uptake and excretion in man, comparative study on pharmacokinetics and metabolism of inhalation anesthetics 853-862

Open-heart surgery, factors affecting A-aDo_2 315-321

respiratory distress with cardiovascular anomaly 481-484

Operating room, fire, potential ignition source 217-218

humidity, Questions and Answers 134

Operating room personnel, effect of anesthetic wastes, Questions and Answers 760

Opthalmology, ketamine and intraocular pressure in children 773-775

pre-and post-anesthetic use of atropine in patients with glaucoma, Questions and Answers 460-461

Oral surgery, cardiovascular effects of cannabinol 203-213

Orthopedics, intraoperative awakening for early recognition of possible neurologic sequelae during Harrington-rod spinal fusion 526-528

Orthopedics, (continued)
monitoring intraoperative spinal cord function 42-44
spinal anesthesia for lumbar disc surgery 550-554
total hip replacement, sodium nitroprusside-induced hypotension 654-662
Otolaryngology, laser microsurgery, fire hazard, Brief Reports 146-147
maxillary sinusitis, nasotracheal intubation, Brief Reports 885-889
Ott M: see Salts L jt auth
Ouabain, general anesthetic agents, and aldosterone effect on striated muscle contraction in toad 409-414
Ouabain tolerance, effect of enflurane, isoflurane, fluroxene, methoxyflurane, and diethyl ether anesthesia in the dog 360-365
Outpatient, comparison of Dot Test and Digit-Symbol Test for street fitness 883-884
dental, prolonged apnea after succinylcholine, Case History 737-739
evaluation, anesthesiologist 307-310
Owens WD: see Muravchick jt auth
Oxygen, anesthetic effect 734-736
Oxygen consumption, effect of $Paco_2$ during cardiopulmonary bypass 269-273
Oxygen toxicity, Case History 588-591
Oxygenation, postoperative, effect of position in markedly obese subjects 37-41
Oxytocic drugs, postpartum hypertension and convulsion 813-815

P

Pacemakers, anesthesia 626
$Paco_2$ effect on oxygen consumption during cardiopulmonary bypass 269-273
$Paco_2$ relation to fresh gas flow, circle system 706-708
Paddleford RR: see Short CE jt auth
Pain, intractable, in adiposis dolorosa, management with intravenous lidocaine 257-259
intractable, use of intrathecal cold saline, Questions and Answers 131-132
relief following acupuncture 229-234
Pancuronium, d-tubocurarine, polymyxin B, and neostigmine, interaction on neuromuscular function 224-228
Pancuronium, influence on potassium efflux produced by succinylcholine 474-477
Pancuronium or d-tubocurarine influence on circulatory responses during thiamylal-N_2O halothane anesthesia 485-488
Pancuronium, prolonged neuromuscular blockade 343-345
Parenteral analgesic activity, butorphanol and morphine 394-401
Parturients, physostigmine reversal of sedation 478-480
Patel K, Bennett EJ, Grundy EM et al: Relation of $Paco_2$ to fresh gas flow in a circle system 706-708
Patel TC: see Geevarghese KP jt auth
Pathology, hepatic in animals sensitized to a halothane metabolite and subsequent halothane exposures 235-242
Paton WDM: see Smith RA jt auth
Patterson RW: Effect of $Paco_2$ on O_2 consumption during cardiopulmonary bypass in man 269-273
Correspondence 898-899
Paulsen AW: see Frazier WT jt auth
Paul WL, Munson ES: Gas embolism during encephalography, Case History 141-145
Paul WL, Munson ES, Maniscalco JE: Cerebrospinal fluid pressure during O_2 encephalography and N_2O inhalation 849-852
Pearsall NN: see Duncan PG jt auth
PEEP device for a manual bag ventilator, Brief Reports 745
Pediatric circle, humidification, Brief Reports 877-879
Pediatric, Jackson-Rees gas scavenger, Brief Reports 881-882
Rees system, safety valve, Brief Reports 741-743
Pediatrics, advantages of infant ventilators over adapted adult ventilators 769-772
bronchial blockade in a child with a bronchopleural-cutaneous fistula using a balloon-tipped catheter, Brief Reports 874-875
congenital lobar emphysema, Case History 869-873
ketamine and intraocular pressure 773-775
nitrous oxide anesthesia, absorption and excretion 95-99
nitrous oxide encephalography 402-408
prevention of hypothermia during cystoscopy, Brief Reports 592-593
prolonged effects of acute ethanol intoxication, neonates, Brief Reports 602-603
radiotherapy, intramuscular ketamine 92-94
Romano-Ward syndrome, effects of stellate ganglion block on the idiopathic prolongation of the Q-T interval with cardiac arrhythmia 782-787
severe hypertension, Wilms' tumor 519-521
unrelenting hypotension associated with an acute abdomen in a comatose hemophiliac child 346-349
"Pentazepam" (pentazocine + diazepam), supplementing local analgesia for laparoscopic sterilization 177-181
Pentazocine + diazepam supplementing local analgesia, laparoscopic sterilization 177-181
Percutaneous cardiovascular catheter introducer, Brief Reports 148-149
Percutaneous transtracheal ventilation, pneumatocele of the larynx, Brief Reports 600-601
Perel A, Eimerl D, Grossberg M: A PEEP device for a manual bag ventilator, Brief Reports 745
Pericardectomy, anesthesia considerations in uremic pericardial effusion 378-382
Perioperative awareness and recall 513-518
Peripheral hemodynamics, effects of doxapram, goats 279-285
Peripheral nerve blocks, arterial and venous plasma levels of bupivacaine 763-768
Perisho JA: see Crawford AH jt auth
Peterson C: see Stoelting RK jt auth
Petty WC: see Blitt CD jt auth
Pflug AE, Aasheim GM, Beck HA: Spinal anesthesia: bupivacaine versus tetracaine 489-492
Pflug AE, Lindop MJ, Murphy TM et al: Early reversal of postoperative hypoxemia 822-828
Pharmacokinetics, uptake and excretion of 1-bromo-1,2,2-trifluorocyclobutane (42M-9) in man 853-862
Pharmacologic basis, local anesthetic agents, obstetrics 829-838
pH dependence of narcotics and narcotic antagonists in clinical anesthesia 253-256

Phenobarbital, halothane MAC in dogs 677-679
Phillips OC: ASA classification, Questions and Answers 615
Physical status classification, Questions and Answers 614-615
Physician and the Law:
$1,237,500 settlement for brain damage during appendectomy 45-46
Anesthetic manufacturer not liable for death of patient 202
No negligence in surgeon's failure to supervise anesthesiologist 459
Physician liability for death of heart transplant donor discussed 611-612
No liability for death of patient during anesthesia 759
Informed consent suit against anesthesiologist 906
Physician-patient relationship, legal aspects of anesthesia, Questions and Answers 463-464
Physician liability in death of heart transplant donor 611-612
Physostigmine reversal of sedation in parturients 478-480
Phytonadione, acute cardiovascular collapse, Brief Reports 304-306
Pig, experimental model, preanesthetic evaluation and management of malignant hyperthermia 643-653
Plasma levels, arterial and venous, bupivacaine 763-768
Plastic surgery, general anesthesia for blepharoplasty and rhytidectomy 165-167
larynx and trachea, carbon dioxide laser microsurgery, fire hazard, Brief Reports 146-147
Pneumatocele of the larynx, a complication of percutaneous transtracheal ventilation, Brief Reports 600-601
Polymyxin-B, d-tubocurarine, pancuronium and neostigmine, interaction on neuromuscular function 224-228
Pontoppidan H: see Fuleihan SF jt auth
Poon YK: A life-threatening complication of cricothyroid membrane puncture, Case History 298-301
Portas MR: see Stanley TH jt auth
Position, lateral sitting, neurosurgery 326-330
semirecumbent versus supine, effect on postoperative oxygenation in markedly obese subjects 37-41
Positive-end-expiratory pressure, ventilator, manual bag, Brief Reports 745
Postoperative hypoxemia, early reversal 822-828
Postpartum hypertension and convulsion after oxytocic drugs 813-815
Post-thoracotomy intercostal block 542-546
Potassium efflux, influence of pancuronium 474-477
Preanesthetic evaluation and management of malignant hyperthermia in the pig 643-653
Precordial ECG lead, chest operations, Brief Reports 740-741
Premedicant, clinical evaluation of injectable lorazepam 522-525
Premedication, lorazepam, lack of recall and relief of anxiety 792-796
Preoperative blood volume measurement, Questions and Answers 275-276
Preoperative evaluation and preparation of the cardiac 618-621
Preoperative testing, outpatients 883-884
Privitera PA: see Boyan CP jt auth
Prolonged neuromuscular blockade associated with trimethaphan 353-356
Prolonged neuromuscular blockade with pancuronium 343-345
Propranolol and isoproterenol, effect on halothane MAC in dogs 383-387
Propranolol, surgical anesthesia 1-5
Protamine, cardiopulmonary bypass 110-113
Pseudocholinesterase, atypical 243-246
Psychology journal articles, fundamental principles for preparation, Editor's Choice 455-458
Pulmonary, absorption-excretion volume effect 51-56
Pulmonary artery catheterization, Brief Reports 148-149
Pulmonary, choice between tracheostomy and prolonged translaryngeal intubation 195-201
congenital lobar emphysema, Case History 869-873
COPD, enflurane anesthesia 806-809
Pulmonary embolectomy, massive pulmonary hemorrhage 182-184
Pulmonary function, effects of post-thoracotomy intercostal block with meperidine 542-546
Pulmonary venous admixture, changes with varying inspired oxygen 688-695

Q

Q-T interval, idiopathic prolongation, effects of stellate ganglion block 782-787
Quadruplet delivery, caudal analgesia 61-66
Questions and Answers: "Torr" origin of the word 131
Intrathecal cold saline solution for intractable pain 131-132
Epidural antibiotics with prolonged catheterization 132-133
Humidity in operating rooms 134
$NaHCO_3$ use with the administration of bank blood 274-275
Preoperative blood volume determination 275-276
Management of patient with hypokalemia on diuretic therapy 276-277
Regional versus general anesthesia 277-278
Pre-and-post anesthetic use of atropine in patients with glaucoma 460-461
Gag reflex 461-463
Physician-patient relationship, legal aspects of anesthesia 463-464
Safety in operation of rechargeable ECG monitor (Tektronix®) 613-614
ASA classification 614-615
Breathalyzer test and exposure to anesthetic gases 615-616
Congenital abnormality in the children of exposed OR personnel 760
Terminology and definition of word "metabolism" 760-761
Balanced anesthesia 907-908
Quimby CW Jr: Physician-patient relationship, legal aspects of anesthesia, Questions and Answers 463-464

R

Rackow H, Salanitre E: The pulmonary absorption-excretion volume effect 51-56
Rackow H: see Salanitre E jt auth
Radiography, evaluation of larynx and trachea, Brief Reports 598-600
pediatric, intramuscular ketamine 92-94

Ramanathan S, Chalon J, Rand P et al: Humidity output of the Columbia pediatric circle, Brief Reports 877-879

Ramanathan S, Chalon J, Turndorf H: A safety valve for the pediatric Rees system, Brief Reports 741-743

Rand P: see Ramanathan S jt auth

Rappolt RT Sr: see Gay GR jt auth

Rats, anesthetic potency of lidocaine 818-821

Ravin MB: How do benefits of hemodilution balance O_2 reduction? Correspondence 898

Rayburn RL: see Ausinsch B jt auth

Rebreathing circuits, hazards, Brief Reports 743-744

Recall and awareness, perioperative 513-518

Recall, absence after general anesthesia 696-701
clinical evaluation of the effect of lorazepam 522-525
lorazepam premedication 792-796

Rees pediatric system, safety valve, Brief Reports 741-743

Regional analgesia, bacteriologic aspects 187-190

Regional anesthesia, bupivacaine 763-768
bupivacaine versus tetracaine 489-492
evaluation of memory 368-373
lumbar disc surgery 550-554
lumbosacral plexus block 350-352
obstetrics 829-838
renal transplantation 69-73

Regional anesthesia versus general, Questions and Answers 277-278

Reimer DH: A life-threatening complication of cricothyroid membrane puncture, Case History Discussion 299-301

Renal failure, neuromuscular blockade with pancuronium 343-345

Renal function and methoxyflurane biotransformation, vaginal delivery or cesarean section 415-419

Renal transplantation, regional anesthesia 69-73

Rendell-Baker L: Some gas machine hazards and their elimination 26-33

Resection, stenotic trachea 191-194

Respiratory and cardiovascular effects of isoproterenol, artifiicial heart implantation 560-567

Respiratory distress, with cardiovascular anomaly 481-484

Respiratory failure, choice between tracheostomy and prolonged translaryngeal intubation 195-201

Respiratory, congenital lobar emphysema, Case History 869-873
COPD, enflurane anesthesia 806-809
inspired air temperature with immersion heater humidifiers 331-334
IPPB, hypoxemia and hypocarbia 555-559
tracheal stenosis 191-194

Respiratory function, effects of post-thoracotomy intercostal block with meperidine 542-546

Restall, CJ: Plastic-covered wire stylet, Correspondence 755

Retrospectroscope . . . the soul of wit, Editor's Choice 900-905

Reversal, protamine, cardiopulmonary bypass 110-113

Reves JG, McCracken LE Jr: Failure to induce hepatic pathology in animals sensitized to a halothane metabolite and subsequently challenged with halothane 235-242

Reves JG: see Laflin MJ jt auth

Rhesus monkeys, cardiovascular effects of enflurane and halothane 85-91
electroanesthesia 536-541

Rhytidectomy and blepharoplasty, general anesthesia 165-167

Rieser JC: pre-and-post anesthetic use of atropine in patients with glaucoma, Questions and Answers 460

Ring WH: see Elwyn RA jt auth

Ritter JG, Anderson N: Comparison of Dot Test and Digit-Symbol Test for street fitness of outpatients 883-884

Ritzman JR, Erickson HH, Miller ED: Cardiovascular effects of enflurane and halothane on the Rhesus monkey 85-91

Roberts RB: see Tausk HC jt auth

Rodriguez R, Gold MI: Enflurane as a primary anesthetic agent for patients with chronic obstructive pulmonary disease 806-809

Rodriguez R: see Moffitt EA jt auth

Roland CG: Thoughts About Medical Writing:
XXXIII. Parallelism is a virtue 139-140
XXXIV. The publication process 261-262
XXXV. "Let's call it hebetization" 366-367
XXXVI. Writing an editorial 534-535
XXXVII. Verify your references 717-718

Romano-Ward Snydrome, effects of stellate ganglion block on the idiopathic prolongation of the Q-T interval with cardiac arrhythmia 782-787

Russo P: see Meltzer HY jt auth

Ryan WP: see Cestone KJ jt auth

S

Sadagopan S: see El-Naggar jt auth

Safety devices, gas machines 26-33

Saka DM, Marx GF: Management of a parturient with cardiac valve prosthesis 214-216

Salanitre E, Rackow H: N_2O volumes absorbed and excreted during N_2O anesthesia in children 95-99

Salanitre E: see Rackow H jt auth

Saline, cold, intrathecal for intractable pain, Questions and Answers 131-132

Salts L, Ott M, Walson PD: Local anesthetic agents—pharmacologic basis for use in obstetrics: a review 829-838

Saluja TS: see Snow JC jt auth

Salvatore A: see Lee JH jt auth

Sari A, Okuda Y, Takeshita H et al: Factors affecting A-aDo_2 after open-heart surgery 315-321

Saviello GM: Cardiac decompensation during enflurane anesthesia in a patient with myotonia atrophica, Case History Comment 435

Schemel WH: Unexpected hepatic dysfunction found by multiple laboratory screening 810-812

Schuhmacher, Lawrence F., Jr: salutation to 753-754

Sedation, physostigmine reversal in parturients 478-480

Seltzer JL, Doto JB, Jacoby J: Decreased arterial oxygenation during sodium nitroprusside administration for intraoperative hypertension, Brief Reports 880-881

Serum potassium, influence of pancuronium on potassium efflux produced by succinylcholine 474-477

Shah NK: see Kripke BJ jt auth

Shephard DAE: Accuracy, brevity, clarity: three principles of good medical writing, Correspondence 893-899

Shnider SM: see Hicks JS jt auth

Short CE, Paddleford RR, McGrath CJ et al: Preanesthetic evaluation and management of malignant hyperthermia in the pig experimental model 643-653

Siker ES: see Cottrell JE jt auth

Silver DJ, Dunsmore RH, Dickson CM: Spinal anesthesia for lumbar disc surgery: review of 576 operations 550-554

Sklar GS, Alfonso AE, King BD: An unusual problem in nasotracheal extubation, Brief Reports 302-303

Smith CA: Management of patient with hypokalemia on diuretic therapy, Questions and Answers 276-277

Smith DB, Clark RB, Stephens SR et al: Physostigmine reversal of sedation in parturients 478-480

Smith NT: see Eger EI II jt auth

Smith RA, Paton WDM: The anesthesia effect of oxygen 734-736

Smith RB: Plasma concentration of lidocaine after endotracheal spray, Correspondence 116-117

Smith RH: see Kano T jt auth

Smith RM: see Sudhir KG jt auth

Snow JC, Norton ML, Saluja TS et al: Fire hazard during CO_2 laser microsurgery on the larynx and trachea, Brief Reports 146-147

Snow JC: Pre-and-post anesthetic use of atropine in patients with glaucoma, Questions and Answers 461

Sodium bicarbonate, use in administration of bank blood, Questions and Answers 274-275

Sodium nitroprusside, induced hypotension 654-662

Sodium nitroprusside-induced hypotension, dosage nomogram 574-581

Sodium nitroprusside, intraoperative hypertension, Brief Reports 880-881

Sokoll MD: Cardiac decompensation during enflurane anesthesia in a patient with myotonia atrophica, Case History Comment 436

Sokoll MD: see Stullken EH jt auth

Spaeth EE: see Link WJ jt auth

Spinal anesthesia, bupivacaine versus tetracaine 489-492

lumbar disc surgery 550-554

Spinal cord function, intraoperative, monitoring using hypnosis 42-44

Spinal fusion, Harrington rod, intraoperative awakening for early recognition of possible neurologic sequelae 526-528

Stanley TH, Hill GE, Portas MR et al: Neutrophil chemotaxis during and after general anesthesia and operation 668-673

Stanley TH: see Liu WS jt auth

Stanton-Hicks M: Epidural antibiotics with prolonged catheterization, Questions and Answers 132-133

Statistics, medical 82-84; 357-359; 846-848

Stedman DH: see Corbett TH jt auth

Stellate ganglion block, effects on the idiopathic prolongation of the Q-T interval with cardiac arrhythmia 782-787

Stephens SR: see Smith DB jt auth

Sterilization, laparoscopic, "pentazepam" 177-181

Stevens WC: Anesthetic management 622-625

Changes in blood chemistries following prolonged enflurane anesthesia, Guest Discussion 549

Stoelting RK:

A dosage nomogram for sodium nitroprusside-induced hypotension under anesthesia, Guest Discussion 574-581

Balanced anesthesia, Questions and Answers 907-908

Gas embolism during encephalography, Case History Comment 143

Influence of pancuronium or d-tubocurarine on circulatory responses during thiamylal-N_2O halothane anesthesia 485-488

see Viegas O jt auth

see Young SR jt auth

Sustained high inspired Po_2 without toxic sequelae, Case History Comment 590

Stoelting RK, Peterson C: Circulatory changes during anesthetic induction: impact of d-tubocurarine pretreatment, thiamylal, succinylcholine, laryngoscopy, and tracheal lidocaine 77-81

Circulatory changes in patients with coronary artery disease following thiamylal-succinylcholine and tracheal intubation 232-234

Stoelting RK, Peterson C, Madura JA: Circulatory responses and halothane concentrations during gastric or gallbladder traction with and without neuromuscular blockade 388-391

Striated muscle contraction, effect of general anesthetic agents, ouabain, and aldosterone, toad 409-414

Stullken EH Jr, Sokoll MD: The effects of heparin on recovery from ischemic brain injuries in cats 683-687

Stylet, plastic covered solid copper wire, Brief Reports 150

Succinylcholine and halothane, massive myglobinuria 680-682

Succinylcholine and thiamylal with d-tubocurarine pretreatment, anesthetic induction 77-81

Succinylcholine, influence of pancuronium on potassium efflux 474-477

prolonged apnea, Case History 737-739

train-of-four fade and edrophonium antagonism of neuromuscular block 663-667

Succinylcholine-thiamylal and tracheal intubation, circulatory changes in patients with coronary artery disease 232-234

Suctioning, catheter tip design 290-297

Sudhir KG, Smith RM, Hall JE et al: Intraoperative awakening for early recognition of possible neurologic sequelae during Harrington-rod spinal fusion 526-528

Summary JJ: see Moore WE jt auth

Supine hypotensive syndrome caused by intra-abdominal mass, Brief Reports 887-889

Surgery, brain damage during appendectomy, Physician and the Law 45-46

hemodynamics, morphine 47-50

isoflurane and halothane, effect on coronary artery disease 135-138

transcervical thymectomy 13-21

Surgical anesthesia and propranolol 1-5

Suwa K: see Yanagida H jt auth

Systolic time intervals, a comparative study of enflurane and halothane 263-268

T

Takacs FA: Single-needle lateral aproach for lumbar sympathetic block, Correspondence 454

Takeshita H: see Sari A jt auth

Takman BH: see Adams HJ jt auth

Talmage EA: Shearing hazard of intra-arterial Teflon catheters, Brief Reports 597-598

Tanifuji Y, Eger EI II: Effect of isoproterenol and propranolol on halothane MAC in dogs 383-387

Tan ST: see Aldrete JA jt auth

Tarhan S: see Cant WF jt auth

see Moffitt EA jt auth

Taub HA, Eisenberg L: An evaluation of memory under regional anesthesia with IV lorazepam as a premedicant 368-373

Tausk HC, Miller R, Roberts RB: Maintenance of body temperature by heated humidification 719-723

Tavakoli M, Corssen G, Caruso FS: Butorphanol and morphine: a double-blind comparison of their parenteral analgesic activity 394-401

Tay CH: see Konchigeri HN jt auth

Taylor FH: see Abouleish E jt auth

Technics, acupuncture 508-512

Carden tube insertion, Brief Reports 882-883

lateral sitting position for neurosurgery 326-330

minimizing tracheal aspiration 816-817

nasogastric tube insertions, Brief Reports 303-304

Tektronix®, safety of operation, Questions and Answers 613-614

Temperature, inspired air with immersion heater humidifiers 331-334

Teske RH: see Adams HR jt auth

Tetracaine versus bupivacaine: spinal anesthesia 489-492

$\triangle^9$ tetrahydrocannabinol, cardiovascular effects during oral surgery 203-213

Tetrodotoxin, local anesthetic activity 568-573

Thiamylal and succinylcholine with d-tubocurarine pretreatment, anesthetic induction 77-81

Thiamylal-succinylcholine and tracheal intubation, circulatory changes in patients with coronary artery disease 232-234

Thiamylal-N_2O halothane anesthesia, influence of pancuronium or d-tubocurarine on circulatory response 485-488

Thomas JD: see Cooke JE jt auth

Thompson DS: see Lawson NW jt auth

Thoracic, gas volume changes 18-21

massive pulmonary hemorrhage complicating pulmonary embolectomy 182-184

post-thoracotomy intercostal block 542-546

resection of stenotic trachea 191-194

Thoracic surgery, endobronchial intubation, intraoperative protection, single functioning lung 340-342

precordial ECG lead, Brief Reports 740-741

Thoughts About Medical Writing:

XXXIII. Parallelism is a virtue 139-140

XXXIV. The publication process 261-262

XXXV. "Let's call it hebetization" 366-367

XXXVI. Writing an editorial 534-535

XXXVII. Verify your references 717-718

Thymectomy, transcervical in myasthenia gravis 13-21

Tinker JH: see Cant WF jt auth

Toad, effect of general anesthetic agents, ouabain, and aldosterone on striated muscle contraction 409-414

Tobey RE: see Laflin MJ jt auth

Tolerance to ketamine 788-791

"Torr," origin of the word, Questions and Answers 131

Total hip replacement, sodium nitroprusside-induced hypotension 654-662

Toxicity, fluroxene 529-533

methylene blue injection, renal blood flow 674-676

oxygen, Case History 588-591

Trachea and larynx, evaluation by xeroradiography, Brief Reports 598-600

Tracheal aspiration, simple technic to minimize 816-817

Tracheal bronchus: unusual airway problem, Brief Reports 746-747

Tracheal intubation and thiamylal-succinylcholine, circulatory changes in patients with coronary artery disease 232-234

Tracheal lidocaine, circulatory changes, anesthetic induction 77-81

Tracheal stenosis, resection 191-194

Tracheobronchial trauma, influence of suction catheter tip design 290-297

Tracheostomy, acute respiratory failure 195-201

Train-of-four fade and edrophonium antagonism of neuromuscular block by succinylcholine in man 663-667

Transcervical thymectomy, anesthesia 13-21

Transplantation, renal, regional anesthesia 69-73

Tranquilizer, memory under regional anesthesia 368-373

Translaryngeal intubation, acute respiratory failure 195-201

Trustman R: see Dubovsky SL jt auth

Tubal ligation, "pentazepam" supplementing local analgesia 177-181

Turndorf H: see Cottrell JE jt auth

see Ramanathan S jt auth

Turner CJ: see Venkateswarlu T jt auth

U

Underwood P, Howland WS: Preoperative blood volume determination, Questions and Answers 275-276

Uremic pericardial effusion, anesthetic considerations for pericardectomy 378-382

Urology, prevention of hypothermia during cystoscopy in neonates, Brief Reports 592-593

V

Vaginal delivery, renal function following methoxyflurane administration 415-419

Vandam LD: On the history of ideas in anaesthesia, Tenth Annual Becton, Dickinson and Company Oscar Schwidetzky Memorial Lecture (1976) 467-473

Van Dyke RA: Terminology and definition of word "metabolism," Questions and Answers 760-761

Vanishing lung syndrome, anesthesia 750-752

Van Nyhuis LS, Miller RD, Fogdall RP: The interaction between d-tubocurarine, pancuronium, polymyxin B, and neostigmine on neuromuscular function 224-228

Vasoconstrictors, action of tetrodotoxin 568-573

Vaughan RW, Bauer S, Wise L: Effect of position (semirecumbent versus supine) on postoperative oxygenation in markedly obese subjects 37-41

Vaughan RW, Wilson SL, Waldbaum LS: Unrelenting hypotension associated with an acute abdomen in a comatose hemophiliac child: a case report 346-349

Vaughan RW: see Cobb ML jt auth

Velazquez JL, Feingold A: Calibration of the Narkotest® gas monitor for isoflurane, Brief Reports 441-442

Venkateswarlu T, Turner CJ, Carter JD et al: The tracheal bronchus: an unusual airway problem, Brief Reports 746-747

Venous pulmonary admixture, changes in oxygen 693-695

Ventilators, advantages of infant over adult in pediatrics 769-772

manual bag, PEEP device, Brief Reports 745

Ventilation, mechanical, end-inspiratory pause, blood-gas exchange 122-130

percutaneous pneumatocele, larynx, Brief Reports 600-601

Viegas O, Stoelting RK: Halothane MAC in dogs unchanged by phenobarbital 677-679

Visual aids, clarity in lecture slides 6-12

W

Wahle WM: see Link WJ jt auth

Waldbaum LS: see Vaughan RW jt auth

Wall J: see Alexander JJ jt auth

Walson PD: see Salts L jt auth

Watson RL: see Moore WE jt auth

Weinreich AI: see Girnar DS jt auth

Weinreich A: see Eisele V jt auth

We Salute: Evan Lloyd Frederickson 67-68

Douglas W Eastwood 185-186

Paul Rudolph Dumke 443-444

Edmond I Eger, II 604-605

Lawrence F Schuhmacher, Jr 753-754

Richard George Barton Gilbert 892

White RD: Drugs in cardiac supportive care 633-639

see Mallow JE jt auth

Wiener EL: see Kennedy PJ jt auth

Wilms' tumor, severe hypertension 519-521

Wilson C: see Johnston RR jt auth

Wilson RD: Balanced anesthesia, Questions and Answers 907-908

Wilson RS: see Fuleihan SF jt auth

Wilson SL, Miller RN, Wright C et al: Prolonged neuromuscular blockade associated with trimethaphan: a case report 353-356

Wilson SL: see Vaughan RW jt auth

Winters WD: Ketamine and epilepsy, Correspondence 449-451

Wise L: see Vaughan RW jt auth

Wolfson B: see Cottrell JE jt auth

Wollman SB, Kushins LG: Survival following massive pulmonary hemorrhage complicating pulmonary embolectomy: a case report 182-184

Wootton DG: see Katz H jt auth

Wright C: see Wilson SL jt auth

Wright FG Jr, Foley MF, Downs JB et al: Hypoxemia and hypocarbia following intermittent positive-pressure breathing 555-559

Wright WA: see Blitt CD jt auth

Writing, copy editors speak out, Editor's Choice 219-223

fundamental principles for preparing psychology journal articles, Editor's Choice 455-458

relationship between author and editor, Editor's Choice 22-25

Wynands JE: Anesthesia for patients with heart block and artificial cardiac pacemakers 626-632

X

Xeroradiography, evaluation of larynx and trachea, Brief Reports 598-600

Y

Yanagida H, Kemi C, Suwa K: The effects of stellate ganglion block on the idiopathic prolongation of the Q-T interval with cardiac arrhythmia (The Romano-Ward syndrome) 782-787

Youngberg JA: Gas embolism during encephalography, Case History Comment 144-145

Young SR, Stoelting RK, Bond VK et al: Methoxyflurane biotransformation and renal function following methoxyflurane administration for vaginal delivery or cesarean section 415-419

Z

Zsigmond EK, Matsuki A, Kothary SP et al: Arterial hypoxemia caused by intravenous ketamine 311-314

Anesthesia AND Analgesia

.....CURRENT RESEARCHES

VOLUME 55, 1976

Journal of the International Anesthesia Research Society

BOARD OF TRUSTEES

International Anesthesia Research Society

Kenneth K. Keown, M.D., *Chairman*

Emerson A. Moffitt, M.D., *Vice Chairman*

B. B. Sankey, M.D., *Executive Secretary*

John T. Martin, M.D.

Dean H. Morrow, M.D.

Edwin S. Munson, M.D.

T. H. Seldon, M.D.

Robert K. Stoelting, M.D.

Paul R. Dumke, M.D., *Emeritus Trustee*

Morris J. Nicholson, M.D., *Emeritus Trustee*

EDITORIAL BOARD

Anesthesia and Analgesia . . . Current Researches

Editor

T. H. Seldon, M.D.

Associate Editors

John T. Martin, M.D.

Emerson A. Moffitt, M.D.

Dean H. Morrow, M.D.

Edwin S. Munson, M.D.

Robert K. Stoelting, M.D.

Contributing Editors

Douglas B. Craig, M.D.

E. Paul Didier, M.D.

Ronald W. Dunbar, M.D.

Leonard C. Jenkins, M.D.

David E. Longnecker, M.D.

John J. Savarese, M.D.

N. Ty Smith, M.D.

Business Manager

B. B. Sankey, M.D.

IN THE NEXT ISSUE

Scientific Articles

Jan.-Feb., 1977

VENTILATORY PATTERN, INTRAPLEURAL PRESSURE, AND CARDIAC OUTPUT—John B. Downs, M.D., Michael F. Douglas, Major, USAF (MC), Peter M. Sanfelippo, Lt. Col., USAF (MC), William Stanford, Colonel, USAF (MC), and Michael R. Hodges, Gainesville, Florida and Lackland AFB, Texas.

IMPLICATIONS OF THE EFFECTS OF GENERAL ANESTHESIA ON BASAL TEAR PRODUCTION—David A. Cross, M.D., and Theodore Krupin, M.D., St. Louis, Missouri and Pensacola, Florida.

ENFLURANE ANESTHESIA FOR SURGICAL REMOVAL OF PHEOCHROMOCYTOMA—Gregory F. Janeczko, M.D., Anthony D. Ivankovich, M.D., Silas N. Glisson, Ph.D., Harold J. Heyman, M.D., and Adel A. El-Etr, M.D., and Ronald F. Albrecht, M.D., Maywood and Chicago, Illinois.

PSRO RECORD-KEEPING SYSTEM FOR ANESTHESIOLOGISTS—Alan W. Grogono, M.D., FFARCS, and Peter B. Kane, M.D., Syracuse, New York.

THE INFLUENCE OF SUCCINYLCHOLINE ON THE DURATION OF PANCURONIUM NEUROMUSCULAR BLOCKADE—Leonard F. Walts, M.D., and William D. Rusin, M.D., Los Angeles, California.

DIFFUSION HYPEROXIA FOLLOWING PREOXYGENATION—R. J. Schuder, M.D., F. R. Weis, Jr., M.D., R. Markello, M.D., E. White, CRNA, and D. Schrader, CRNA, Buffalo, New York.

CHANGES IN RENAL BLOOD FLOW FOLLOWING SODIUM NITROPRUSSIDE IN PATIENTS UNDERGOING NEPHROLITHOTOMY—Alexander A. Birch, M.D., and William H. Boyce, M.D., Winston-Salem, North Carolina.

THE EFFECT OF SPONTANEOUS VS CONTROLLED VENTILATION ON THE RATE OF RISE OF ALVEOLAR HALOTHANE CONCENTRATION IN DOGS—Robert T. Gibbons, M.D., Eugene P. Steffey, V.M.D., Ph.D., and Edmond I. Eger, II, M.D., San Francisco, California and Kansas City, Missouri.

COMPARISON OF THAM AND SODIUM BICARBONATE IN RESUSCITATION OF THE HEART AFTER VENTRICULAR FIBRILLATION IN DOGS—Max Minuck, M.D., and G. P. Sharma, M.D., Winnipeg, Manitoba, Canada.

THERMOREGULATORY DEFECT IN RATS DURING ANESTHESIA—Ben A. Hitt, Ph.D., Richard I. Mazze, M.D., Thomas L. Cook, M.D., William J. Beppu, M.D., and Jon C. Kosek, Palo Alto, California.

AUTONOMIC BLOCKADE AND THE CARDIOVASCULAR AND CATECHOLAMINE RESPONSE TO ELECTROSHOCK—A. H. Anton, Ph.D., D. S. Uy, M.D., and C. L. Redderson, M.D., Cleveland, Ohio.

DYNAMICS OF COMPOUNDED LOCAL ANESTHETIC MIXTURES IN REGIONAL ANESTHESIA—P. Prithvi Raj, M.D., Jordan Miller, M.D., Edward Carden, M.D., and Ronald L. Katz, M.D., Los Angeles, California.

IS THE BAIN BREATHING CIRCUIT THE FUTURE ANESTHESIA SYSTEM? AN EVALUATION—Young K. Chu, M.D., Kang H. Rah, M.D., and C. Paul Boyan, M.D., Richmond, Virginia.

ISOFLURANE ANESTHESIA AND PRESSURE ANTAGONISM IN MICE—D. W. Kent, M.D., M. J. Halsey, D.Phil., and E. I. Eger, II, M.D., San Francisco, California.

IMPROVED OXYGENATION DURING THORACOTOMY WITH SELECTIVE PEEP TO THE DEPENDENT LUNG—David R. Brown, M.D., Enid R. Kafer, M.D., FRACP, FFARCS, Virgil O. Roberson, M.D., Benson R. Wilcox, M.D., and Gordon F. Murray, M.D., Chapel Hill, North Carolina and Sydney, Australia.

CORRELATION OF PLASMA CHOLINESTERASE ACTIVITY AND DURATION OF ACTION OF SUCCINYLCHOLINE DURING PREGNANCY—Casey D. Blitt, M.D., W. Clayton Petty, M.D., Eva Alberternst, CRNA, and Barbara J. Wright, Tucson, Arizona.

SPONTANEOUS RECOVERY FROM NONDEPOLARIZING NEUROMUSCULAR BLOCKADE CORRELATION BETWEEN CLINICAL AND EVOKED RESPONSES—Jeffrey B. Brand, M.D., David J. Cullen, M.D., Norman E. Wilson, M.D., and Hassan H. Ali, M.D., Boston, Massachusetts.

LACK OF CNS DEPRESSION FROM LARGE DOSES OF TRIMETHAPHAN IN SHEEP—K. C. Wong, M.D., Ph.D., Jeffrey L. Peters, Ph.D., M.D., Theodore S. Roberts, M.D., James C. McRea, B.D., and Hiroyuki Fukumasu, M.D., Salt Lake City, Utah and Kyoto, Japan.

EFFECT OF HALOTHANE AND PENTOBARBITAL ANESTHESIA ON THE DISPERSION OF INDICATOR PARTICLES PASSING THROUGH THE CENTRAL CIRCULATION OF A DOG—Guy G. Davis, Jr., M.D., Ph.D., A. William Paulsen, M.M.Sc., and Evan L. Frederickson, M.D., Atlanta, Georgia.

CASE HISTORY #94.

BRIEF REPORTS:

FIBEROPTIC LARYNGOSCOPE GUIDE AND PROTECTOR—Jen F. Wang, M.D., Birmingham, Alabama.

COMPRESSED AIR-O_2-ANESTHETIC MIXTURES FOR THE NEONATE—J. Frederick Jones, M.D., and Richard J. Hendershot, LCDR, USNR (MC), Portsmouth, Virginia and Washington, D.C.

A SIMPLE METHOD FOR VERIFYING ENDOTRACHEAL TUBE PLACEMENT—Ercument A. Kopman, M.D., St. Louis, Missouri.

A WARMER FOR ANTISEPTIC SKIN PREPARATION SOLUTIONS—Charles J. Restall, M.D., and Steven P. Schmidt, CRNA, Rochester, Minnesota.

CANNULATION OF A NON-PALPABLE ARTERY WITH THE AID OF A DOPPLER MONITOR—Chana Buakham, M.D., and Jong Min Kim, M.D., Kansas City, Missouri.

ACUTE PULMONARY EDEMA FOLLOWING HEAD INJURY: TWO CASE REPORTS—Harry B. Cohen, M.D., and G. W. N. Eggers, Jr., M.D., Columbia, Missouri.

PROGESTERONE FOR THE PICKWICKIAN SYNDROME: RESPIRATORY IMPLICATIONS—Ray McKenzie, M.D., FFARCS, and Rajindar K. Wadhwa, M.D., Pittsburgh, Pennsylvania.

FLUCTUATING HYPOXEMIA AND PULMONARY SHUNTING FOLLOWING FATAL HEAD TRAUMA. CASE REPORT—Nathan L. Pace, M.D., Seattle, Washington and Fort Sam Houston, Texas.

A Guide for Authors

Anesthesia and Analgesia . . . Current Researches invites manuscripts on subjects pertinent to the specialty of Anesthesia.

Send manuscripts and illustrations in *triplicate* to:

T. H. Seldon, MD, Editor
Kahler East, Suite C
Rochester, Minnesota 55901

Four categories of reports will be considered for publication.

1. Original articles describing clinical or laboratory research.

2. Brief Reports describing new anesthetic technics, equipment, clinical, or laboratory studies.

3. Case Reports.

4. Letters-to-the-Editor.

EDITORIAL POLICIES

Peer review.—All papers submitted are reviewed by selected referees with respect to validity, pertinence, completeness, and originality. If accepted for publication, editorial revisions may be made to aid clarity and understanding. Edited copy will be submitted to authors for approval before the paper goes to the printer. Pageproofs also will be submitted to the authors for final approval. Reprint order forms will accompany pageproofs.

Cover letter.—A letter must accompany each manuscript, stating that the work has not been simultaneously submitted to another journal or previously published in part or whole. The name and address of the author to whom correspondence may be directed should be given.

Legal and ethical considerations.—Information or illustrations which might permit identification of patients must not be used.

Reports describing data from experiments performed on humans must contain a statement in the Methods section, when appropriate, that written informed consent and/or institutional approval of the investigation has been obtained, and that procedures involving the use of animals was conducted so as to minimize discomfort.

Excerpts from material published elsewhere must be accompanied by written permission from the author and publisher to reproduce the material.

JOURNAL STYLE

Format.—All portions of the manuscript should be typewritten and double-spaced, including lists of reference citations. Each component of the paper (title page, with authors' academic rank and addresses, Introduction, Methods, Results, Discussion, References, Legends) should begin on a separate page. Original articles must be preceded by an Abstract concisely describing the purpose, methods, results, and conclusions. Abstracts should not exceed 1 typewritten page in length. Brief Reports and Case Reports do not require an Abstract, but a Summary at the end may be appropriate.

Original articles should be concise (not over 3000 words) and present new information pertinent to anesthesia. Preliminary reports or fragments of material that may better be included in a single, more detailed, report should not be submitted. Brief Reports describing new equipment or technics should present new advances, with advantages over the alternatives. Descriptions of new equipment must be sufficient to permit the reader to either construct or purchase the equipment. Case Reports should emphasize important clinical conditions or variations in typical patient responses. Letters-to-the-Editor must be brief (250-500 words) and should offer constructive comments on

recently published articles or discuss areas of general interest to anesthesiologists.

Measurement units.—The metric system should be used for all such data as length, mass, volume, and temperatures. Torr should be used in place of mm Hg for partial pressures. Authors are encouraged to adopt the International System of units (moles per liter rather than mg percent) for concentrations or amounts of substances. (See Padmore GRA, Nunn JF: SI Units in relation to anaesthesia. A review of the present position. Br J Anaesth 46:236-243, 1974).

Drug names.—Generic or chemical drug names are required. Brand names may be inserted in parentheses after the generic name, if pertinent.

Abbreviations.—The first time an abbreviation appears it should be preceded by the full word it represents.

Respiratory symbols.—Symbols for respiratory physiology should be defined the first time used and should follow Pappenheimer J et al: Standardization of definitions and symbols in respiratory physiology. Fed Proc 9:602-605, 1950.

References. — References should correspond to Index Medicus style and should be listed in the same numerical order as they appear in the text. Reports that are not accessible to all readers or that have not undergone editorial review (abstracts, correspondence, or personal communications) should not be included in numerical listings but may be footnoted. They should include pertinent addresses as well as source and authors' names.

Illustrations.—Drawings and photographs (unmounted glossy prints) should be numbered in order of appearance in the manuscript and labeled on the back with the first author's name and indicate the top edge of the picture.

Tables.—These should carry a title or caption and should supplement, not duplicate, the text.

51ST CONGRESS

International Anesthesia Research Society

MARCH 6-10, 1977

DIPLOMAT RESORT AND COUNTRY CLUBS
HOLLYWOOD, FLORIDA

Anesthesia and Analgesia CURRENT RESEARCHES

BACK ISSUES AVAILABLE

Available at $3.00 Per Issue

Vol.	Year	Numbers Available						Vol.	Year	Numbers Available					
33	1954	–	2	3	4	5	6	41	1962	–	2	3	–	5	6
34	1955	1	–	3	4	5	6	42	1963	–	–	3	4	5	6
35	1956	1	2	3	–	–	6	43	1964	–	2	–	–	–	6
36	1957	–	–	–	–	–	6	44	1965	–	2	3	4	5	6
37	1958	1	2	3	4	5	6	45	1966	–	2	–	–	–	6
38	1959	–	2	3	4	–	6	46	1967	–	–	3	–	–	6
39	1960	–	–	3	4	5	6	47	1968	–	–	3	4	5	6
40	1961	–	–	3	4	5	6	48	1969	1	2	3	–	5	–

Available at $4.50 Per Issue

Vol.	Year	Numbers Available						Vol.	Year	Numbers Available					
49	1970	1	–	–	–	5	6	53	1974	–	2	3	4	–	–
50	1971	1	2	3	–	–	–	54	1975	1	2	–	–	–	–
51	1972	–	2	3	–	–	6	55	1976	–	2	3	4	5	
52	1973	1	2	3	4	–	–								

SINGLE ISSUES PRIOR TO 1954: Write to publisher at address below for listing of issues available at $2.00 each.

BOUND VOLUMES AVAILABLE: $8.00—For Years 1947, 1948, 1949; $10.00—For Years 1953, 1955

OTHER PUBLICATIONS AVAILABLE:

"Basic and Clinical Physiology of the Liver" (Supplement to Sept.-Oct. 1965 issue)—$3.00.

Ten-Year (1960-1969) Cumulative Index—$3.00.

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, Ohio 44122

Please send me the publications circled above, or listed hereunder:

☐ Check for $_____ enclosed.

☐ Please send bill with understanding that ordered material will be sent when payment is received.

Name_____

Address_____

City, State, Zip_____

AT LAST! CLEAN AIR!

PED-EVAC™ Gas Evacuator

FOR INFORMATION WRITE TO:

PED-EVAC Company
Post Office Box 752
Port Angeles, Washington 98362

PRECISE, ECONOMICAL, SAFE...

RALS POWER UNIT

...INSTANT ATOMIZATION FOR FAST TOPICAL ANESTHESIA

Fast, measured topical anesthesia is ready at your finger tips in a Rals Power Unit. Forget about pumping bulbs, uneven atomization, and limited spraying duration. The Rals Power Unit uses a non-toxic propellant, dichlorodifluoromethane (freon) to activate standard DeVilbiss Atomizers No's. 151, 152 and 163. Instantly, a fine mistlike spray is produced. A graduated solution vial is available for measuring the amount of solution administered.

The Rals Power Unit has been proven effective in cocainization prior to endotracheal intubation, endoscopic instrumentation, laryngotracheal insufflation, and in a variety of nose and throat procedures.

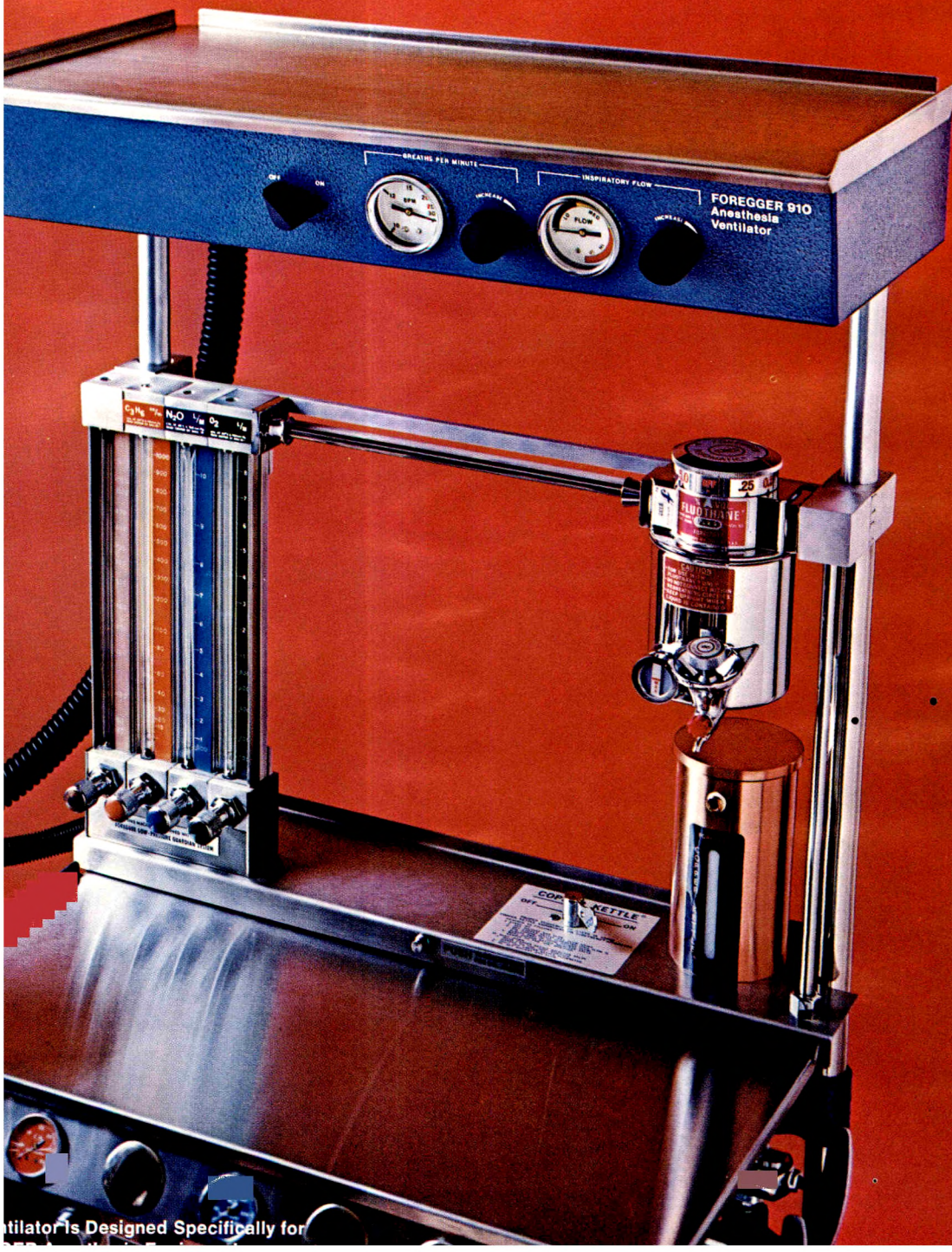
Rals Power Unit #168 are supplied six to a box with adaptor top and metal base. Illustration shows #152 atomizer. All styles in stock.

WRITE OR PHONE FOR LITERATURE, PRICE LIST.

RALS LABORATORIES DIVISION
SCHUEMANN *Laboratories, Inc.*
480 WEST AURORA ROAD • NORTHFIELD, OHIO 44067

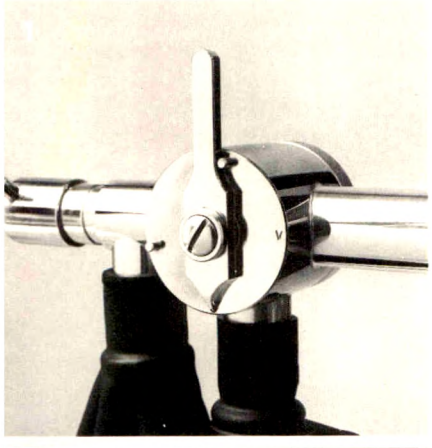
SL-45

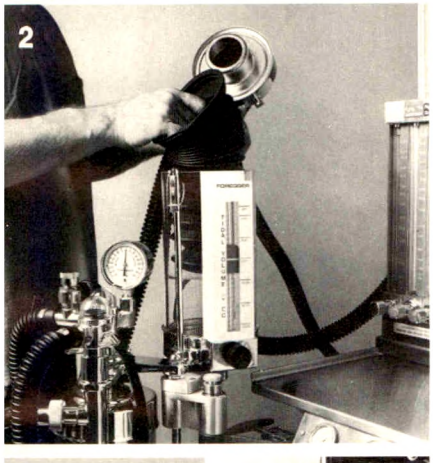
Get Quiet, Simple Performance That's Out of Your Way

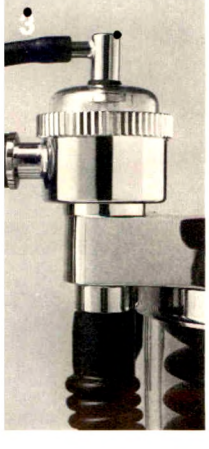


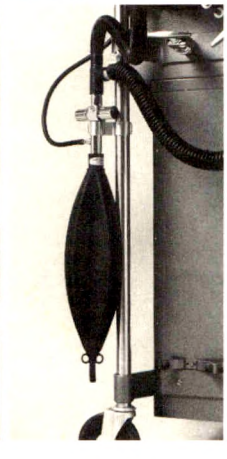
tilator Is Designed Specifically for

The FOREGGER® 910 Anesthesia Ventilator









Your job is complicated enough! You administer anesthesia, chart the patient's vital signs, monitor blood loss and blood gases, regulate the I.V., and much more. In short, you have plenty to do. Therefore, you may use an anesthesia ventilator to help maintain patient control.

But adding on a ventilator can mean adding on distractions, especially if it requires control adjustments for parameters you may not even need. And, you can end up settling for a complicated ventilator arrangement that is inconvenient to use.

So we developed the human-engineered FOREGGER 910 Anesthesia Ventilator. Human-engineered because it gives you just the ventilation control you need in a compact, convenient, uncomplicated package. And it's built-in. So it's accessible, but not in the way.

Simple to operate. Simple to monitor. Simple to clean and maintain. And it's quiet. In addition, the 910 Ventilator helps control OR pollution with an efficient gas collection system.

For additional information contact your Air Products Representative, FOREGGER dealer, or write to Air Products and Chemicals, Inc., Customer Service Department, Box 538 M, Allentown, Pa. 18105.

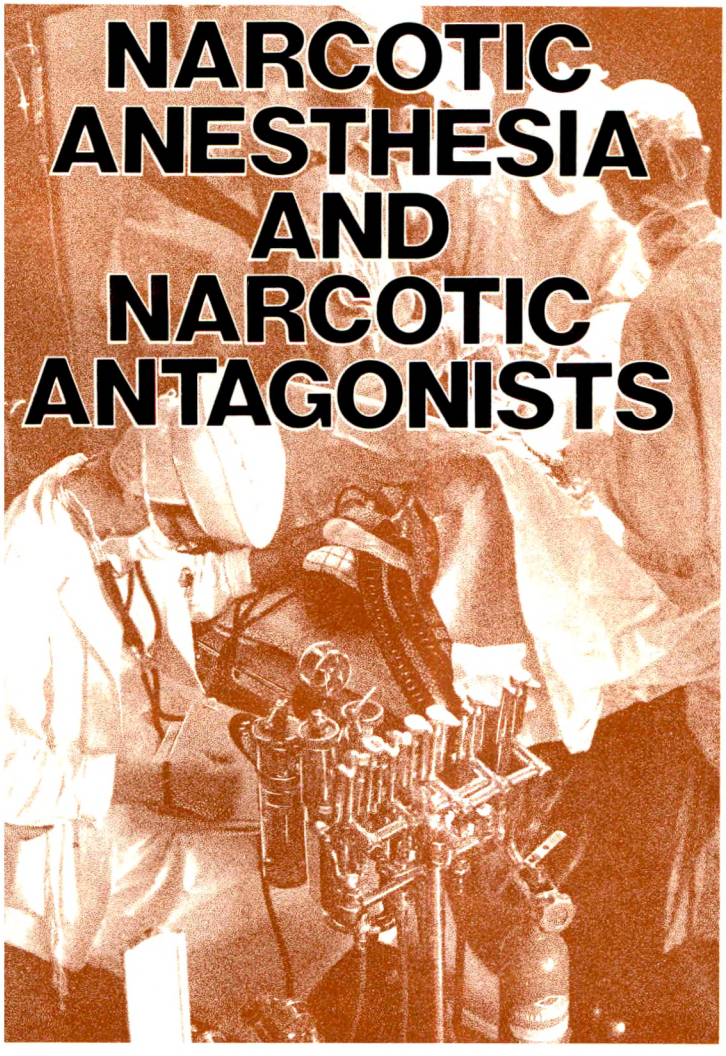
Simple to Monitor because built-in, easy-to-read gauges show Breaths Per Minute, Tidal Volume and Inspiratory Flow at a glance, without clock-watching or computing. And the ventilator control panel is positioned to give you clear visibility and direct control from a comfortable working position.

1. Simple to Operate because it's built-in and requires only five simple steps to initiate and control ventilation. Switches from "bag" to ventilator at a touch.

2. Simple to Clean and Maintain because the bellows and bellows dome container can be easily removed for cleaning, sterilizing and drying purposes. And fluidic circuitry minimizes maintenance.

3. Helps to Minimize OR Pollution because excess gas is automatically vented into a built-in gas evacuator.

Air Products
FOREGGER



NARCOTIC ANESTHESIA

- Despite many advantages, the use of opioids to supplement nitrous oxide anesthesia may be associated with significant postoperative depression.

NARCAN® (naloxone HCl)

- Narcan® in sufficient doses will antagonize opioid effects, including all degrees of respiratory depression and analgesia.
- The degree of narcotic antagonism exhibited by NARCAN® is dose dependent.

A recent study of surgical patients receiving narcotic-nitrous oxide anesthesia was undertaken to determine whether careful titration of naloxone would reverse post-operative narcotic depression and maintain a subjective level of analgesia.[1]

THE OBJECTIVES:

- Restore consciousness
- Reverse narcotic-induced respiratory depression as evidenced by $PaCO_2$
- Maintain *subjective* analgesia

THE METHOD:

- 12 unpremedicated patients received INNOVAR® (fentanyl/droperidol) 5-10 ml I.V. followed by thiopental for induction. Anesthesia was maintained with N_2O-O_2. Increments of 0.1 mg *fentanyl* were given I.V. every 10 minutes during surgery.

Following the procedure, naloxone (0.1 mg/ml) was given in 0.1 mg I.V. increments at 1 minute intervals until the patient was awake, lucid and had adequate tidal and minute volumes. Additional naloxone

eisterkamp DV, Cohen PJ. *Anesth Analg* (Cleve) 53:12-18, Jan-Feb 1974
RCAN® is an Endo registered U.S. trademark; U.S. Pat. 3,254,088

was given I.V. as needed in the first 6 patients; a second group of 6 patients received supplemental naloxone I.M. 30 minutes after the initial I.V. dose.

- 11 patients received 10 mg *morphine* I.M., as well as secobarbital and atropine, 1½ hours preoperatively. Anesthesia was induced by 30 mg morphine given slowly I.V. followed by thiopental and was maintained by N_2O-O_2. Additional morphine was given in divided increments to total 1 mg/kg in the first hour. Further morphine was given as needed. For initial narcotic reversal, naloxone was given as above except at 2 minute intervals. Supplemental naloxone was given I.M. 30 minutes later.

THE RESULTS (fentanyl group):

- When fentanyl was used as the sole narcotic supplement during anesthesia, an I.M. dose of naloxone equal to half the I.V. reversal dose and given ½ hour later provided adequate narcotic reversal.

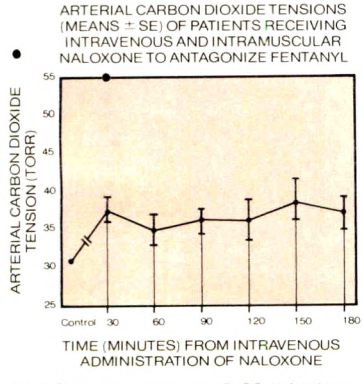


Fig. 1. Control and postoperative $PaCO_2$ in 6 patients receiving I.V. and I.M. naloxone following fentanyl

THE RESULTS (morphine group):

- "After other narcotics, such as morphine, an I.M. dose of naloxone equal to the I.V. dose appears appropriate."

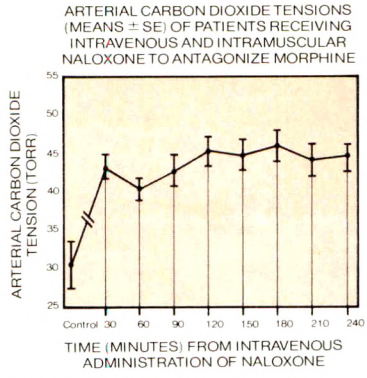


Fig. 2. Control and postoperative $PaCO_2$ in 11 patients receiving I.V. and I.M. naloxone following morphine

THE CONCLUSIONS:

- "Naloxone provides fast, potent, and reliable antagonism to narcotic-induced respiratory depression."
- "By careful titration, this antagonism can be achieved while acceptable analgesia is maintained."
- "Both morphine and fentanyl groups had adequate analgesia, with only 2 patients [of total 21] requiring pain medication in the recovery room."

- **reverses all degrees of narcotic-induced respiratory depression**
- **does not cause narcotic-like effects**
- **does not augment non-narcotic depression**
- **acts rapidly—generally withi 2 minutes following I.V. use and slightly less rapidly whe given I.M.**
- **does not lead to tolerance**
- **does not produce psychotomimetic effects or pupillary constriction**
- **can be repeated if initial dos doesn't produce desired degree of narcotic reversal and improvement in respiratory function**
- **following satisfactory response patient should be observed closely and given repeat doses, if necessary, since the duration of action c some narcotics may exceed that of NARCAN®**

Please see next page for complete prescribing information.

Endo Laboratories, Inc
Subsidiary of E.I. du Pont de Nemours & Co. (In
Garden City, N.Y. 11530

DUPONT

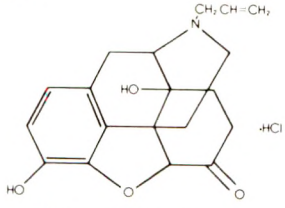
·restored consciousness
·reversed narcotic-induced respiratory depression
·maintained subjective analgesia

NARCAN®
(naloxone HCl)

can reverse narcotic-induced respiratory depression while maintaining subjective analgesia

NARCAN® (naloxone HCl)

DESCRIPTION NARCAN® (naloxone hydrochloride), a narcotic antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



NALOXONE HYDROCHLORIDE
(N-allyl-nor-oxymorphone HCl)

Naloxone hydrochloride occurs as slightly off-white crystals, and is soluble in water, slightly soluble in alcohol and practically insoluble in ether.

NARCAN® (naloxone hydrochloride) Injection is available in two concentrations, 0.02 mg and 0.4 mg of naloxone hydrochloride per ml. Each ml of either strength contains 8.6 mg of sodium chloride; and 2.0 mg of methylparaben and propylparaben as preservatives in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

ACTIONS NARCAN® (naloxone hydrochloride) is an essentially pure narcotic antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists; NARCAN® (naloxone hydrochloride) does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists it exhibits essentially no pharmacologic activity.

In the presence of physical dependence on narcotics NARCAN® (naloxone hydrochloride) will produce withdrawal symptoms; it has not been shown to produce tolerance nor to cause physical or psychological dependence.

When NARCAN® (naloxone hydrochloride) is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of NARCAN® (naloxone hydrochloride). Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of NARCAN® (naloxone hydrochloride), however, will also be dependent upon the amount, type and route of administration of the narcotic being antagonized.

INDICATIONS NARCAN® (naloxone hydrochloride) is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by natural and synthetic narcotics, propoxyphene and the narcotic-antagonist analgesic pentazocine.
NARCAN® (naloxone hydrochloride) is also indicated for the diagnosis of suspected acute opiate overdosage.

CONTRAINDICATIONS NARCAN® (naloxone hydrochloride) is contraindicated in patients known to be hypersensitive to it.

WARNINGS NARCAN® (naloxone hydrochloride) should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN® (naloxone hydrochloride) should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride).

NARCAN® (naloxone hydrochloride) is not effective against respiratory depression due to non-opioid drugs.

Usage in Pregnancy Safe use of NARCAN® (naloxone hydrochloride) during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or other embryotoxic effects (See ANIMAL PHARMACOLOGY AND TOXICOLOGY). However, NARCAN® (naloxone hydrochloride) should be administered to pregnant patients only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS In addition to NARCAN® (naloxone hydrochloride), other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

In an isolated report two patients with pre-existing ventricular irritability requiring lidocaine, and either isoproterenol or epinephrine for hypotension following cardiopulmonary bypass procedures, developed ventricular tachycardia or fibrillation when given NARCAN® (naloxone hydrochloride) I.V. at 9 and 14 hours, respectively, postoperatively for persistent unresponsiveness. Although a direct cause and effect relationship has not been established, NARCAN® (naloxone hydrochloride) should be used with caution in patients with cardiac irritability.

ADVERSE REACTIONS In rare instances nausea and vomiting have been reported in postoperative patients receiving NARCAN® (naloxone hydrochloride) in doses higher than that recommended; a cause and effect relationship has not been established.

DOSAGE AND ADMINISTRATION NARCAN® (naloxone hydrochloride) may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride) the patient should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary.

USAGE IN ADULTS Narcotic Overdose—Known or Suspected The usual initial adult dose is 0.4 mg (1 ml) NARCAN® (naloxone hydrochloride) administered I.V., I.M. or S.C. If the desired degree of counteraction and improvement in respiratory function is not obtained immediately following I.V. administration, it may be repeated intravenously at 2 to 3 minute intervals. Failure to obtain significant improvement after 2 or 3 doses suggests that the condition may be due partly or completely to other disease processes or non-opioid drugs.

Post Operative Narcotic Depression For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN® (naloxone hydrochloride) are usually sufficient. The dose of NARCAN® (naloxone hydrochloride) should be titrated according to the patient's response. Excessive dosage of NARCAN® (naloxone hydrochloride) may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or tachycardia.

For the initial reversal of respiratory depression, NARCAN® (naloxone hydrochloride) should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal i.e., adequate ventilation and alertness without significant pain or discomfort.

Repeat doses of NARCAN® (naloxone hydrochloride) may be required within one to two hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

USAGE IN CHILDREN Narcotic Overdose—Known or Suspected The usual initial child dose is 0.01 mg/kg body weight given I.V., I.M. or S.C. This dose may be repeated in accordance with the adult administration guideline. If necessary, NARCAN® (naloxone hydrochloride) can be diluted with sterile water for injection.

USAGE IN NEONATES Narcotic-induced depression The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines.

HOW SUPPLIED 0.4 mg/ml of NARCAN® (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration.

Available in 1 ml ampuls in boxes of 10 and 100.

0.02 mg/ml of NARCAN® (naloxone hydrochloride) NEONATAL INJECTION for intravenous, intramuscular and subcutaneous administration.

Available in 2 ml ampuls in boxes of 10 and 100 ampuls.

ANIMAL PHARMACOLOGY AND TOXICOLOGY In the mouse and rat the intravenous LD_{50} is 150 ± 5 mg/kg and 109 ± 4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the LD_{50} (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injections; no toxic effects were seen at 10 mg/kg/day for 3 weeks.

Reproductive studies including fertility, general reproductive performance, embryotoxicity, teratogenicity, and lactation did not show any abnormality in mice and rats at 10 mg/kg/day.

NARCAN® (naloxone hydrochloride) Ampuls
Stocked in Military Depot, NSN 6505-00-079-7867

Endo Laboratories, Inc.
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DUPONT

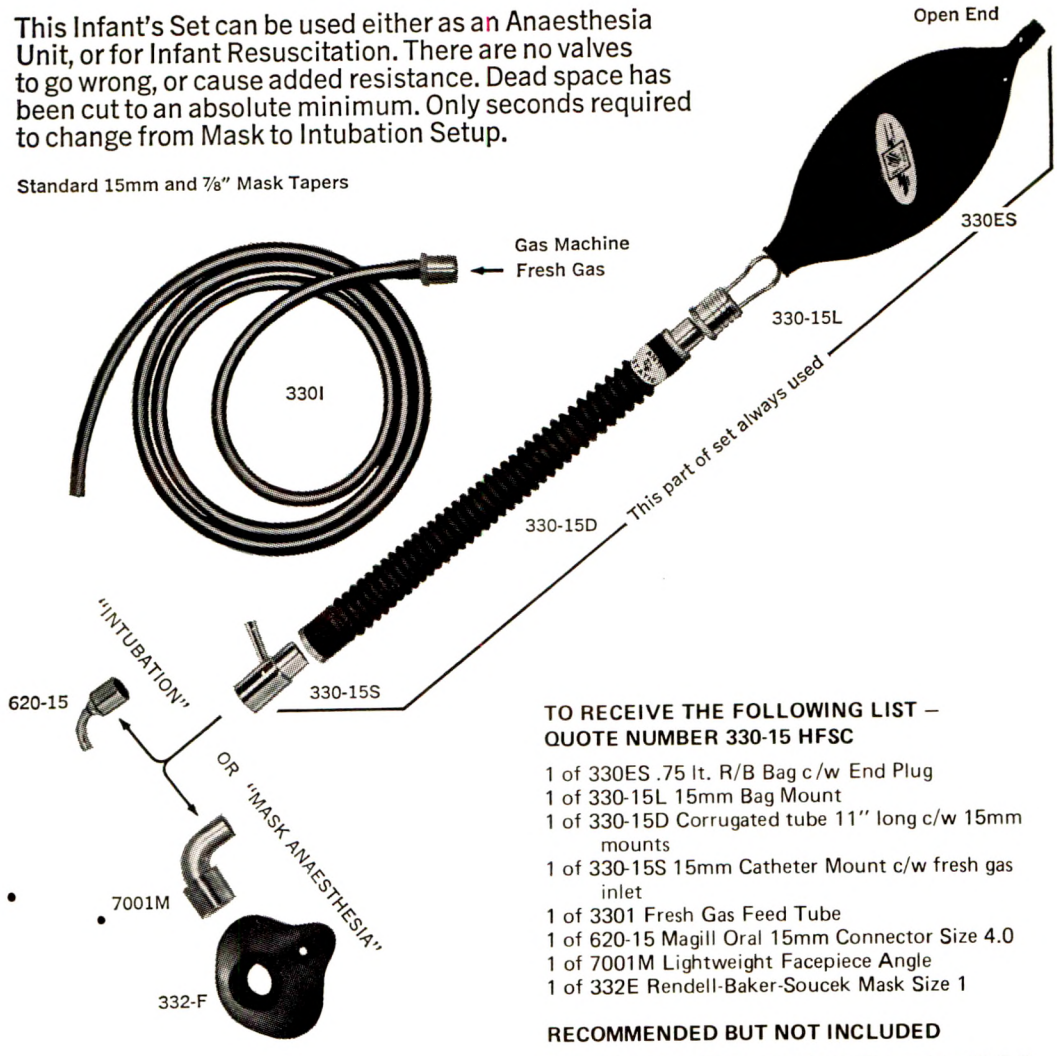
76-1 EDO-6040

JACKSON-REES MODIFICATION OF AYRE'S T-PIECE

as used by leading children's hospitals

This Infant's Set can be used either as an Anaesthesia Unit, or for Infant Resuscitation. There are no valves to go wrong, or cause added resistance. Dead space has been cut to an absolute minimum. Only seconds required to change from Mask to Intubation Setup.

Standard 15mm and 7/8" Mask Tapers



We recommend you purchase a 330LC Leather Case to store this equipment — prevents loss or damage.

TO RECEIVE THE FOLLOWING LIST — QUOTE NUMBER 330-15 HFSC

1 of 330ES .75 lt. R/B Bag c/w End Plug
1 of 330-15L 15mm Bag Mount
1 of 330-15D Corrugated tube 11" long c/w 15mm mounts
1 of 330-15S 15mm Catheter Mount c/w fresh gas inlet
1 of 3301 Fresh Gas Feed Tube
1 of 620-15 Magill Oral 15mm Connector Size 4.0
1 of 7001M Lightweight Facepiece Angle
1 of 332E Rendell-Baker-Soucek Mask Size 1

RECOMMENDED BUT NOT INCLUDED

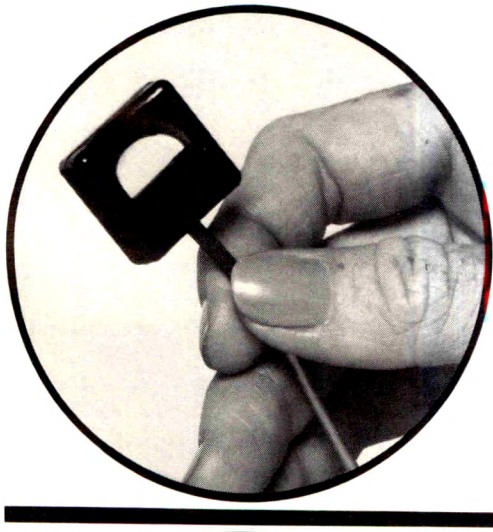
6 (1 each) 330CF Foregger Coles Tubes 8 to 18 F.G.
1 No. 332F Rendell-Baker-Soucek Mask Size 2
1 No. 332L Rendell-Baker-Soucek Mask Size 3
1 330LC Leather Case
1 of 330-15D Corrugated tube c/w 15mm mounts.

MIE

MEDICAL & INDUSTRIAL EQUIPMENT
A division of Claudius Ash Incorporated
655 - 73rd Street, Niagara Falls, New York 14304

SEND FOR COMPLETE LITERATURE

VERSATONE® MULTI-PURPOSE DOPPLER INSTRUMENT

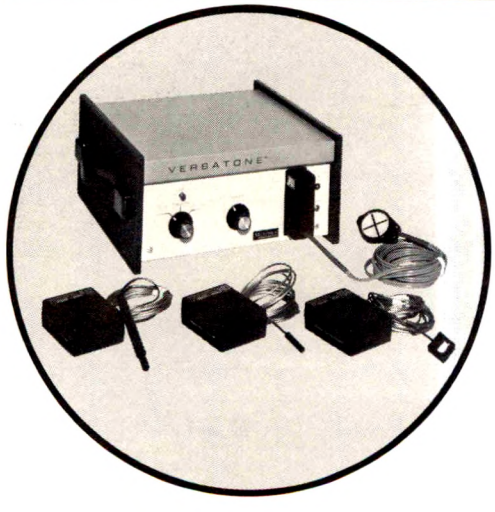


FOR MONITORING DOPPLER SOUNDS OF BLOOD FLOW AND TO TAKE DOPPLER SYSTOLIC BLOOD PRESSURE

This sensitive Doppler probe is easy to tape in position for non-invasive detection and monitoring of arterial blood flow during surgery. Used with an occlusive cuff and manometer, systolic blood pressures may be obtained even on infants and hypotensive patients.

FOR EARLY DETECTION OF VENOUS AIR EMBOLISM

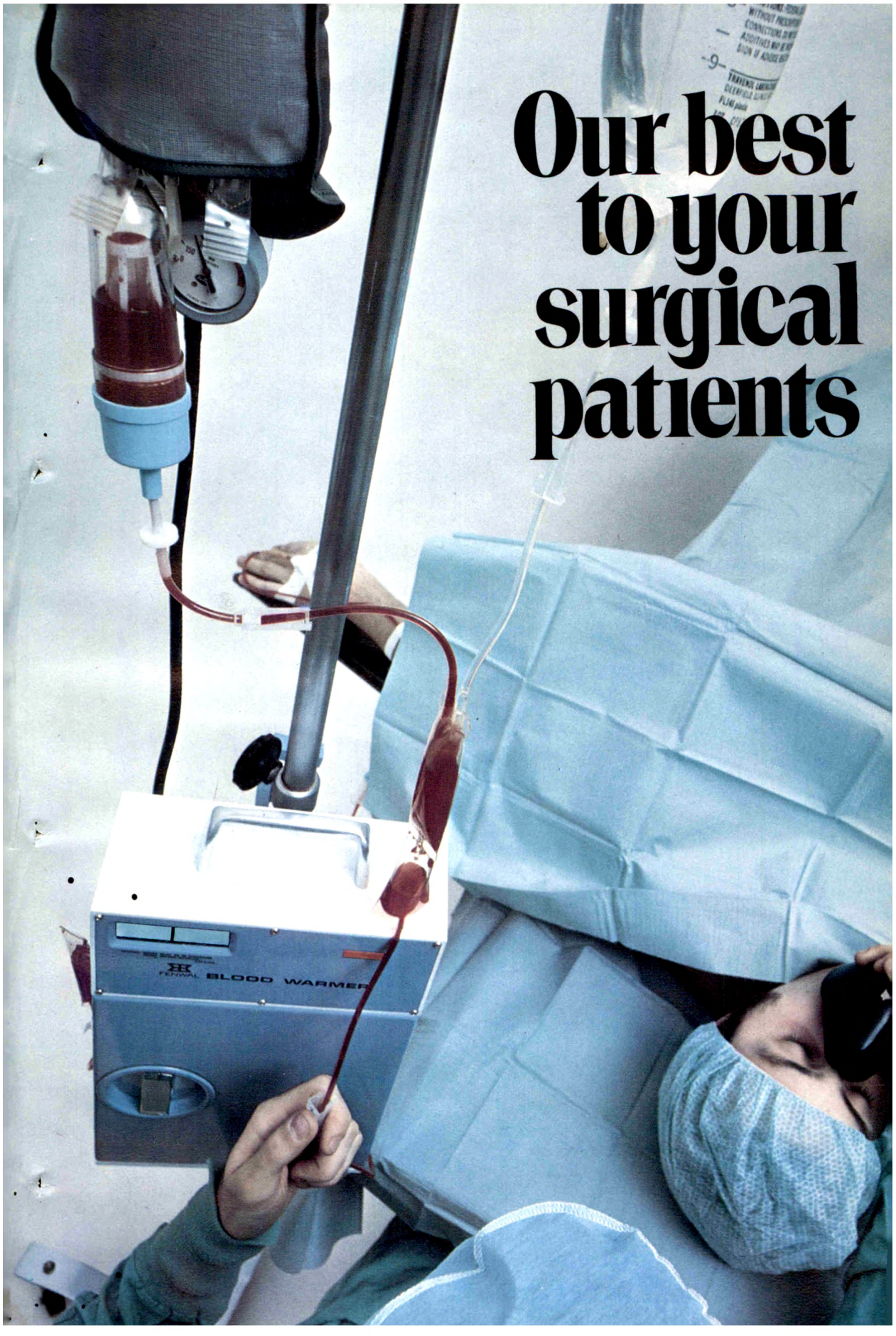
This sensitive wide-angle Doppler probe is particularly well suited for the detection of venous air emboli which may occur during neurosurgical procedures performed with the patient in the upright position. It also detects motion of the heart muscle, heart valves and blood flow.



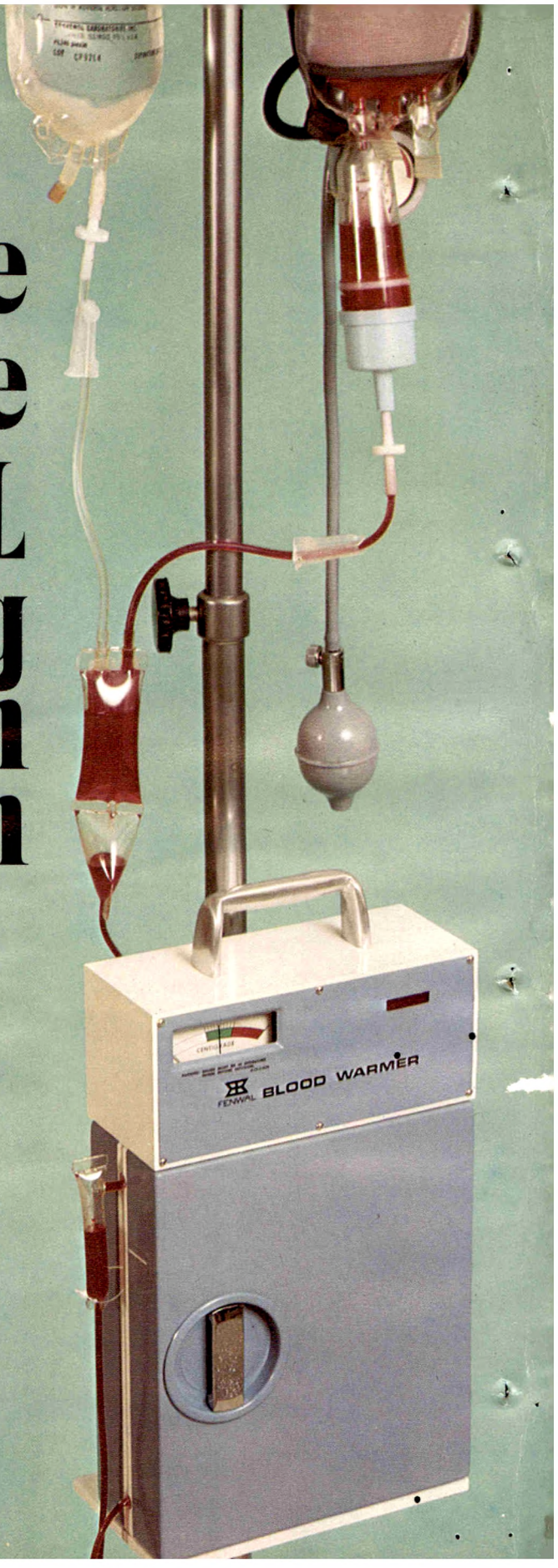
VERSATONE D8 DOPPLER

The Model D8 VERSATONE Doppler instrument is designed to use interchangeable probes of various frequencies and configurations. It is powered by a rechargeable battery and has a built-in loudspeaker. Options include an electrocautery sensor and cut-out, a molded earset for private listening, and a chart recording circuit. The two probes shown above are particularly useful to the anesthesiologist. Two sizes of pencil shaped probes are also available. These are useful for intraoperative assessment of flow in exposed vessels, as well as for transcutaneous flow detection.

MED SONICS
For more information call or write:
P.O. Box M (340 Pioneer Way) Mountain View, CA (415) 965-3333


Our best
to your
surgical
patients
FENWAL BLOOD WARMER

The complete FENWAL operating room system



The Fenwal Dry Heat Blood Warmer is designed for use during single or multiple transfusions when precise regulation of blood temperature and flow rate is indicated. It utilizes a disposable plastic blood-warming pathway.

Fenwal Recipient Sets are available to accommodate your infusion requirements. The Single Lead Set is to be used for the intravenous administration of one unit of whole blood, red cells or plasma. The "Y" Recipient Set is designed to permit dual hookups for simultaneous administration of blood and/or solutions. The Triple Lead Set may be employed in multiple infusion procedures, i.e., blood, solutions, blood components and medication.

The Fenwal Microaggregate Blood Filter is designed to remove microaggregates down to 20 microns in size during intravenous administration of stored whole blood or red cells.

Fenwal Pressure Infusors provide an efficient non-air-dependent method for the rapid infusion of whole blood or red cells.

The Fenwal TYPENEX™ Blood Recipient Identification System ties together the identity of the transfusion candidate, his cross-match request form, blood sample and up to 10 cross-matched units of blood.

The Fenwal Venous Pressure Manometer Set is a disposable, preassembled unit that permits continuous monitoring of the patient's venous pressure while performing one simple hookup.

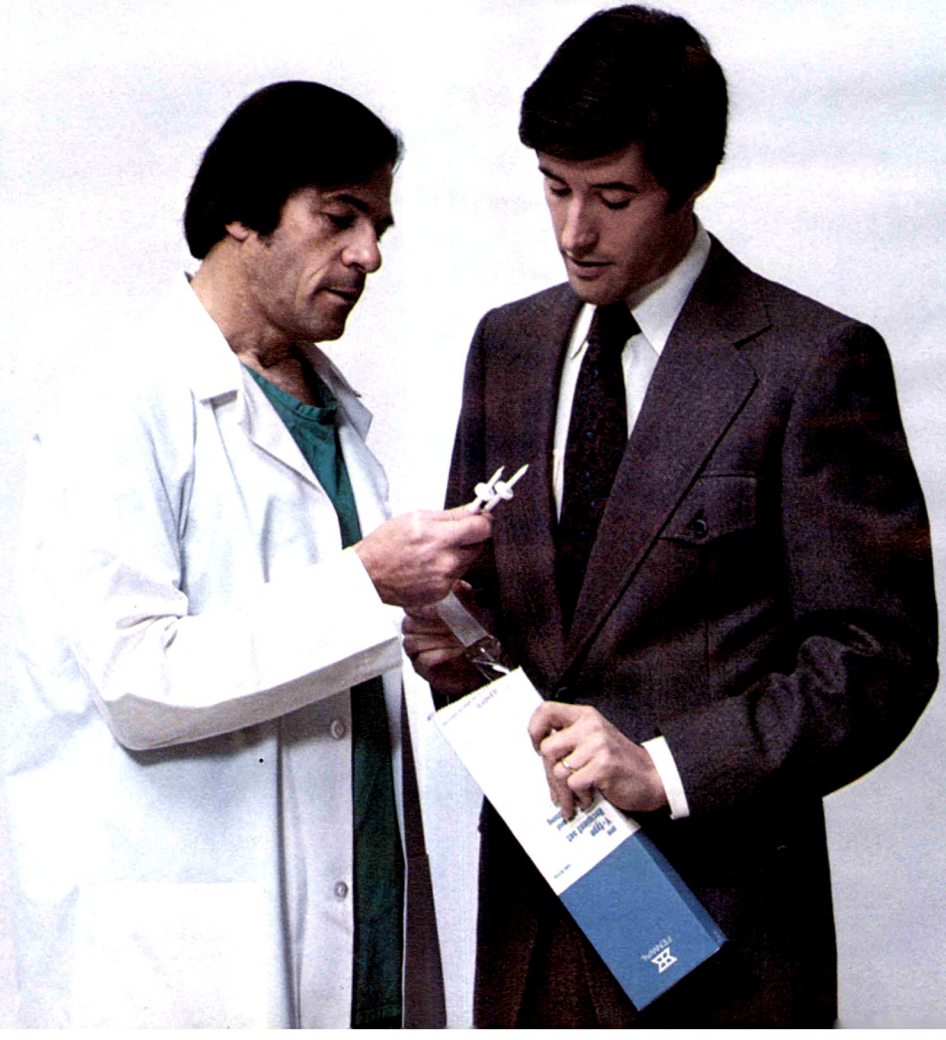
The Fenwal Platelet Recipient Set is designed specifically for the infusion of fresh blood and pool platelet concentrates.

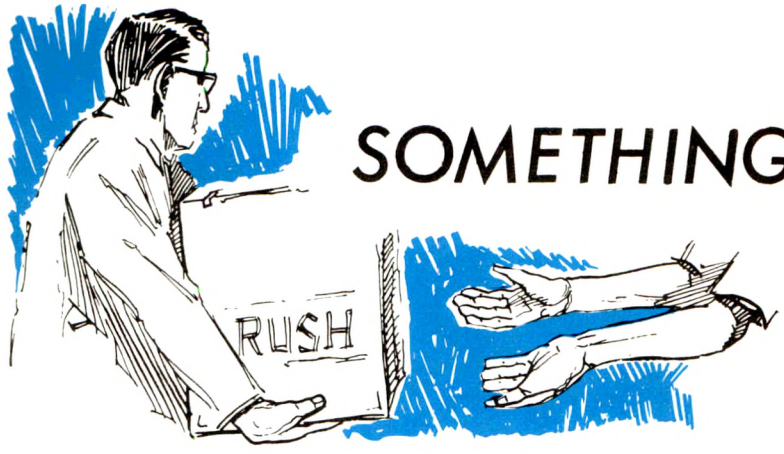
Our best to you

Fenwal Laboratories has long been identified with innovation in modern blood handling systems. Our knowledge and experience in developing and providing sophisticated blood processing systems have earned a reputation for excellence. Thoroughly researched and tested to meet the demands of the medical profession, you can expect the same quality in Fenwal operating room devices that helped achieve our recognition with the nation's blood banks.

The Fenwal Specialist in your hospital can provide you and the other members of the operating team with completely detailed information on all of our products. Intensive training makes him fully qualified to answer your most involved questions regarding up-to-date blood transfusion procedure. Be sure to see your Fenwal Specialist the next time he visits your department.

FENWAL LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois, U.S.A. 60015

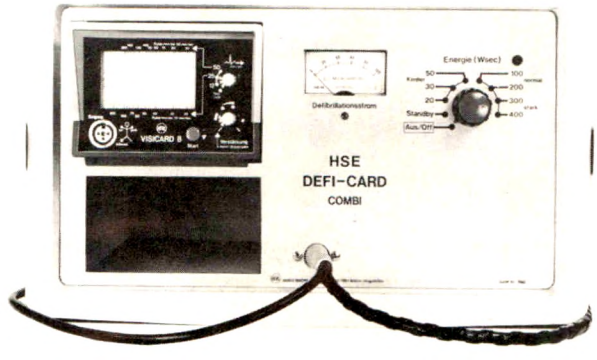




SOMETHING NEW

The Resuscitation Laboratories, Bridgeport, Connecticut, has available the DEFI-CARD-COMBI, a new compact portable battery operated DC defibrillator for emergency use.

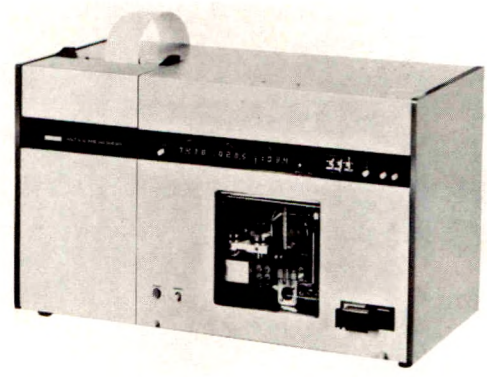
The DEFI-CARD-COMBI may be used in COMBI-nation with the VISICARD 8 for monitoring the patient using the paddles as electrodes. In the "stand-by" position, the ECG is obtained without charging the defibrillator. Cardiac activity may be observed before and after defibrillation.



The self-powered VISICARD 8 may be instantly removed from the DEFI-CARD-COMBI and applied directly to the chest for spot monitoring. Once the defibrillator is charged, a recharging circuit guarantees the availability of the energy regardless of the interval between setting and discharge.

★ ★ ★

American Hospital Supply is introducing Writer Electrode Gel, an ECG electrolyte designed for any area of the hospital which uses a conductive gel for cardiac testing. According to the manufacturer, Writer Gel provides clear traces and rapid baseline stability—but without the use of suspended gritty particles sometimes found in other gels. Writer Gel is slow drying, uses a lanolin base and is lemon scented.



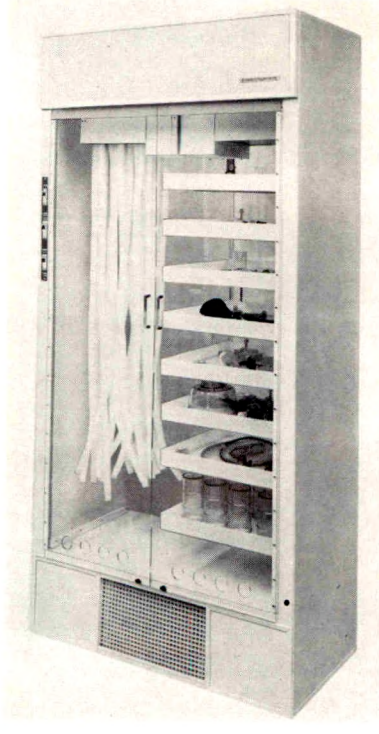
Radiometer's new ABL2 Acid-Base Laboratory is being introduced by The London Company, the exclusive U. S. representative for Radiometer Copenhagen.

This new second generation system features automatic operation, complete analysis with micro samples of blood, patient temperature input, easy-change membranes for the blood gas electrodes, built-in electronic barometer and advanced self-diagnosis testing programs. The ABL2 also contains the advanced features of the ABL1 system which include measured hemoglobin, patented liquid calibration, gas mixer which utilizes a single cylinder of inexpensive CO_2 and room air to furnish precise calibration gas mixtures.

The totally automated operation includes calibration measurement, computation, rinsing and printout.

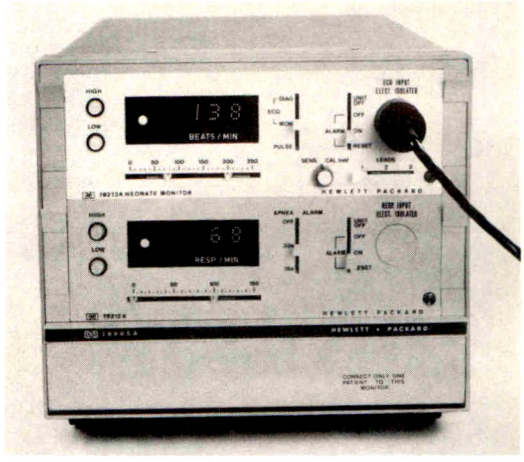
Direct measurements determine the patient's hemoglobin, pH, Pco_2 and Po_2 from the blood microsample. These measurements are simultaneously used by the computer to calculate additional parameters, including actual bicarbonate, standard bicarbonate, total CO_2, base excess, standard base excess and oxygen saturation. Special patient-temperature conditions can be easily dialed into the ABL2. A permanent record is provided by the built-in printer.

★ ★ ★



Olympic Medical Corp, Seattle, Washington, has available a new Model 40 Olympic Sterile-Drier with a larger capacity, high speed, bio-clean drier for wet disinfected respiratory therapy and anesthesia equipment. A new concept in drying cabinets, all air entering the Model 40 passes through HEPA (High Efficiency Particulate Air) filters. Each Model 40 Olympic Sterile-Drier is individually tested at the factory with a particle counter and meets standards for Class 100, bio-clean air (no more than 100 particles larger than 0.5 microns per cubic foot of air). The Model 40 will dry 24 tubes and 8 parts trays or converts quickly to dry 48 tubes or 16 parts trays. Double, full-length, see-through doors provide easy access.

Hewlett Packard Medical Electronics Division, Waltham, Massachusetts, has a new neonatal heart-rate monitor, specifically designed to detect ECG signals from infants. The HP 78213A plug-in module, which measures heart rate in the range of 20 to 250 beats per minute, features high sensitivity that allows detection of the often steeply rising, low-amplitude QRS complexes in premature infants.



The neonatal heart-rate monitor has electrically isolated patient input which effectively isolates the newborn from potential hazardous leakage currents. Heart rate is displayed digitally by bright, light-emitting-diode numerals.

Because the vector of the neonate's ECG changes, the module contains a lead selector as standard to allow the attending staff to select the best setup for reliable monitoring. Audible and visual alarms alert the medical staff when the monitored infant's heart rate deviates beyond preselected limits for more than 8 seconds.

ADDRESS CHANGE NOTICE

International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, Ohio 44122

Please change my mail address for ANESTHESIA and ANALGESIA . . . Current Researches, effective

_____:

FROM—(Current or former address)

_____
Street Address

_____
City, State, Zip Code

Important: Show your name and address exactly as your Journal is now addressed.

TO—(New Address)

_____
Street Address

_____
City, State, Zip Code

_____
Print Your Name

The local that gives you the longest anesthesia gives your patient longer postoperative analgesia.

Marcaine® hydrochloride (brand of bupivacaine hydrochloride)—available with or without epinephrine—is the local anesthetic that provides the longest duration of action among commonly used local anesthetics. Which minimizes the problems of "continuous" technique or repeat doses.

Marcaine also provides longer postoperative analgesia. Which reduces the need for postoperative narcotics.

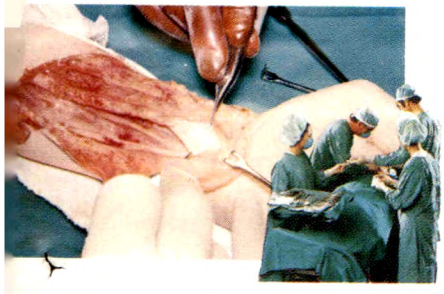
And in data in over 3,000 patients, Marcaine was reported to have excellent or satisfactory results in more than 96% of cases.

Extended anesthesia for the surgeon

In regional blocks, Marcaine, with or without epinephrine, usually provides anesthesia at least 1½ to 2 times longer than lidocaine or mepivacaine. And approximately 20% longer than tetracaine.

In fact, anesthesia may extend up to 9 hours for peridural block and up to 12 hours for peripheral nerve block. This has been established in several thousand surgical and obstetrical patients.[1-4]

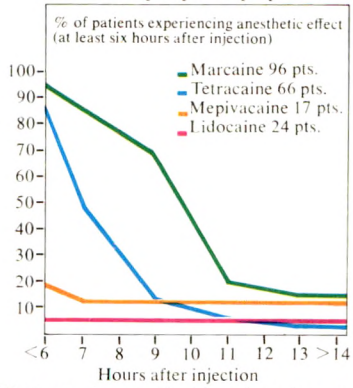
In fact, a single Marcaine epidural injection, with or without epinephrine, may be enough for up to 3½[4] or more[5] hours of anesthesia for surgery, and often provides analgesia that carries over into the recovery room and beyond. When necessary, doses may be repeated up to once every three hours. Caution is advised in administration of repeat doses to patients with severe liver disease. Until further experience is gained, total daily dose of



400 mg. should not be exceeded nor is administration to children under 12 recommended. Also see epinephrine warnings and precautions statements on next page.

This longer anesthetic action can minimize problems of "continuous" technique or repeat doses. Thus, there is the further advantage of a reduced likelihood of introducing infection since injections are less frequent.[6]

Chart I
Duration of anesthesia
Percentage of patients experiencing anesthetic effect—
Comparison of Marcaine with epinephrine and other local anesthetic/epinephrine preparations*



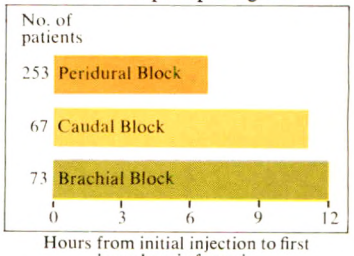
*Equipotent doses used for bilateral, simultaneous blocks of sciatic/femoral, intercostal, or brachial/axillary nerves. Adapted from Moore, D. C.: Data in the files of the Sterling-Winthrop Research Institute.

Extended postoperative analgesia for the patient

Marcaine, with or without epinephrine, gives your patient more—considerably more—postanesthetic analgesia than other local anesthetics in various types of nerve block.[3,4,7,8] An analgesia that persists after the return of motor function and even cutaneous sensation.[7] As a result, you may be able to defer[1,5] and sometimes even eliminate,[5] postoperative narcotics. Chart II illustrates the average duration of time between the initial Marcaine injection and the need for postop analgesics. Many of the 67 patients given Marcaine, with or without epinephrine, caudally for rectal surgery did not complain of pain for 11 hours or longer following induction.

In another group of 40 patients[8] given Marcaine or mepivacaine, both with epinephrine, locally for tonsillectomy, Marcaine pain relief lasted 3 to 5 times longer than that provided by mepivacaine. And in a study[1] of 65 patients given 0.5% Marcaine with epinephrine caudally for rectal or other perineal surgery, complete sensation returned in a mean of 8½ hours for the average patient. And the majority of these patients did not require a narcotic for an additional 1 to 3 hours.

Chart II
Duration of time between injection of Marcaine, with or without epinephrine, and need for postop analgesics†



†Average—exclusion of extremes and failures. Adapted from Lund, P.C., *et al.*: *Anesth. Analg.* 49:103, Jan.-Feb. 1970.

Excellent clinical acceptance

Marcaine, with or without epinephrine, was administered to 3,112 patients for various types of local anesthesia.[9] Of these patients, only 2 experienced a systemic reaction. Although Marcaine has a very wide safety margin, adverse reactions characteristic of those associated with other amide local anesthetics may occur.

Marcaine is indicated for most anesthetic blocks; however, until further clinical experience is gained, paracervical block is not recommended.

See important product information concerning warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations on next page.

Extends the limits of time in anesthesia[1-4]
Extends the limits of time in postoperative analgesia[3,4,7,8]

Marcaine® hydrochloride

Brand of
bupivacaine hydrochloride

with or without epinephrine 1:200,000

Winthrop

MARCAINE® Hydrochloride
Brand of **bupivacaine hydrochloride**

Indications: Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

Contraindication: Marcaine is contraindicated in patients with known hypersensitivity to it.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. Reproduction studies have been performed in rats and rabbits and there is no evidence of harm to the animal fetus. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions: The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Adverse Reactions: Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings).

Allergic reactions, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

References: 1. Moore, D. C., Bridenbaugh, L. D., Bridenbaugh, P. O., *et al.*: Bupivacaine, a review of 2,077 cases, *J.A.M.A. 214*:713, Oct. 26, 1970. **2.** Moore, D. C., Bridenbaugh, L. D., Bridenbaugh, P. O., *et al.*: Bupivacaine for peripheral nerve block: a comparison with mepivacaine, lidocaine and tetracaine, *Anesthesiology 32*:460, May 1970. **3.** Hollman, A.: Axillary plexus block: a double-blind study of 59 cases using mepivacaine and LAC-43, *Acta Anaesthesiol. Scand., Suppl. 21*:53, 1966. **4.** Bromage, P. R.: A comparison of bupivacaine and tetracaine in epidural anesthesia for surgery, *Can. Anaesth. Soc. J. 16*:37, Jan. 1969. **5.** Lund, P. C., Cwik, J. C., and Vallesteros, F.: Bupivacaine—a new long-acting local anesthetic agent, a preliminary clinical and laboratory report, *Anesth. Analg. 49*:103, Jan.-Feb. 1970. **6.** Wise, G. F.: Guest Discussions, *Anesth. Analg. 49*:113, Jan.-Feb. 1970. **7.** Moore, D. C.: Data in the files of the Sterling-Winthrop Research Institute. **8.** Puento-Egido, J. J., Dudeck, J., and Nolte, H.: The clinical use of the local anesthetic agent Marcaine (Carbostesin®), *Anaesthesist 16*:224, August 1967. **9.** Data in the files of the Sterling-Winthrop Research Institute. (1664MB)

Winthrop

Winthrop Laboratories, New York, N.Y. 10016

FORMULA

PRODUCT IDENTIFICATION			MULTIPLE DOSE VIAL						SINGLE DOSE AMPUL				
Marcaine HCl (brand of bupivacaine HCl)		Epinephrine* (as bitartrate)	Methylparaben	Sodium Bisulfite	Thioglycerol	Ascorbic Acid	60% Sod. Lactate	Edetate Calcium Disodium	Sodium Bisulfite	Thioglycerol	Ascorbic Acid	60% Sod. Lactate	Edetate Calcium Disodium
%	mg./ml.	Dilution	mg./ml.	mg./ml.	ml./ml.	mg./ml.	ml./ml.	mg./ml.	mg./ml.	ml./ml.	mg./ml.	ml./ml.	mg./ml.
0.25	2.5	—	1	—	—	—	—	—	—	—	—	—	—
0.25	2.5	1:200,000	1	0.5	.001	2	.0017	0.1	.5	.001	2	.0017	0.1
0.5	5.0	—	1	—	—	—	—	—	—	—	—	—	—
0.5	5.0	1:200,000	1	0.5	.001	2	.0017	0.1	.5	.001	2	.0017	0.1
0.75	7.5	—							—	—	—	—	—
0.75	7.5	1:200,000	Not Available in Vials						.5	.001	2	.0017	0.1

Note: The pH of these solutions is adjusted with sodium hydroxide or hydrochloric acid. Sodium chloride has been added to make each solution isotonic.

*Solutions of Marcaine that contain epinephrine should not be autoclaved.

Federal law prohibits dispensing without a prescription.

Extends the limits of time in anesthesia[1-4]
Extends the limits of time in postoperative analgesia[3,4,7,8]

Marcaine® hydrochloride

Brand of

bupivacaine hydrochloride

with or without epinephrine 1:200,000

air) after a 2-month hospitalization. One month later, however, she developed an osteomyelitis of several ribs on the left side and underwent rib resection. A pneumatocele followed by a bronchopleural-cutaneous fistula was treated 3 months later and again in 4 months. Organisms cultured included *Pseudomonas* and *Staphylococcus aureus*.

The patient's first admission to this hospital was in January 1975. She was a chronically ill appearing child with marked clubbing of the fingers and toes. She had 2 left chest tubes open to air, draining purulent material. A Valsalva maneuver would produce copious secretions and air bubbles from the tube. Bronchoscopy and bronchography revealed a fistula from the distal left mainstem bronchus to a large empyema cavity at the base of the left lung, and also lingular bronchiectasis. Operation consisted of decortication of the left upper lobe, removal of the empyemic left lower lobe cavity, and a subtotal lingular excision.

Anesthetic management involved induction with halothane by mask and spontaneous ventilation, with minimal gas escape from the fistula. This was followed by careful local anesthetic spray to the pharynx, larynx, and trachea. A 4-mm Storz ventilating bronchoscope was then placed in the left mainstem bronchus with the tip beyond the orifice of the left upper lobe bronchus. A 7-FG balloon-tipped arterial embolectomy catheter was then placed in the left mainstem bronchus through the bronchoscope which was then withdrawn from the trachea but left surrounding the Fogarty catheter and kept on the operating table. The trachea was then intubated with a #5 endotracheal tube, positioning the Fogarty catheter external and posterior to the tube.

Ventilation of the lungs was now attempted with the endotracheal tube in place and the Fogarty balloon uninflated. A good portion of the ventilation was seen to be emerging from the fistula. The Fogarty catheter balloon was inflated with 2.5 ml of air, a seal being demonstrated by the easy ventilation of both lungs and the absence of gas bubbles at the fistula. This seal was thus obtained without the necessity of inserting the endotracheal tube into the right mainstem bronchus, and ventilation of the left upper lobe was thus continued throughout the procedure.

Dissection of adhesions required approximately 2 hours, during which the Fogarty catheter effectively sealed the bronchus. The catheter was removed when the surgeon could clamp the bronchus directly. The patient was extubated in the operating room and has had a benign postoperative course, being discharged 12 days postoperatively with all chest tubes removed. She was followed for 10 months without recurrence of difficulty.

DISCUSSION

Positioning of the diseased lung uppermost contributed materially to the technical success of the operation. With positive-pressure ventilation, the uppermost lung is preferentially ventilated, and with an open bronchopleural-cutaneous fistula, much of the ventilation would have been wasted. Blocking the affected bronchus gave control of infective secretions, adequate control of ventilation, and optimal surgical position.

The Fogarty balloon-tipped catheter remained in place for almost 2 hours, the bronchus remaining gastight during that time. With the control thus achieved, an unhurried careful dissection probably minimized blood loss. The length of the catheter enabled the bronchoscope to be kept alongside the patient with the catheter still inside. Should the balloon have slipped out of the bronchus into the trachea, the bronchoscope could have been easily reinserted and the catheter repositioned. The Fogarty embolectomy catheter is commonly available in the operating suite and seems well suited to the occasional need for bronchial blockade.

Selective bronchial blockade in children using this balloon-tipped catheter has been described by others.[1-4] In 2 cases,[1,2] bronchi were blocked with the Fogarty catheter and patients recovered uneventfully, although this is not conclusive evidence that the blocker had indeed protected the involved lung from infective secretions. Our report is unique because of the demonstration that the bronchus was sealed to gas by the Fogarty catheter.

REFERENCES

1. Vale R: Selective bronchial blocking in a small child. Br J Anaesth 41:453-455, 1969

2. Hogg CE, Lorhan PH: Pediatric bronchial blocking. Anesthesiology 33:560-562, 1970

3. Lines V: Selective bronchial blocking in a small child (correspondence). Br J Anaesth 41:893, 1969

4. Cay DL, Csenderits LE, Lines V, et al: Selective bronchial blocking in children. Anaesth Intensive Care 3:127-130, 1975

Difficult Extubation of an Endotracheal Tube Cuff

THIEN YEW NG, MD*
TAPAN D. DATTA, MD†
Pittsburgh, Pennsylvania‡

EXTUBATION after short-term intubation is not usually difficult. However, untoward incidents can occur, as illustrated by the following report.

REPORT OF A CASE

A 61-year-old woman, 165 cm tall and weighing 55 kg, was admitted for left Keller arthroplasty and interphalangeal fusion of the 2nd toe. Preoperative medication consisted of 75 mg of meperidine, 50 mg of hydroxyzine, and 0.4 mg of atropine IM. Anesthesia was induced with 240 mg of thiamylal IV, followed by 80 mg of succinylcholine, which provided good relaxation for a smooth orotracheal intubation with a lubricated 36 French red-rubber Murphy tube. The tube cuff was inflated until there was no leak, inflation requiring 3 ml of air. Anesthesia was maintained with N_2O-O_2 (60:40) and intermittent doses of fentanyl and d-tubocurarine.

At the end of operation, the patient's tracheobronchial tree and mouth were suctioned and the cuff was deflated. When extubation was attempted, the endotracheal tube seemed caught after withdrawal of several centimeters. The tube could be pushed down easily but came to an abrupt stop when it reached one particular level on attempted extubation. The patient was asked to hold her breath in deep inspiration and the tube was removed with some difficulty.

Examination of the endotracheal tube showed a collar-like ridge or "flange" at the lower part of the cuff (figure). The patient recovered uneventfully except for a "sore throat" lasting 2 days.

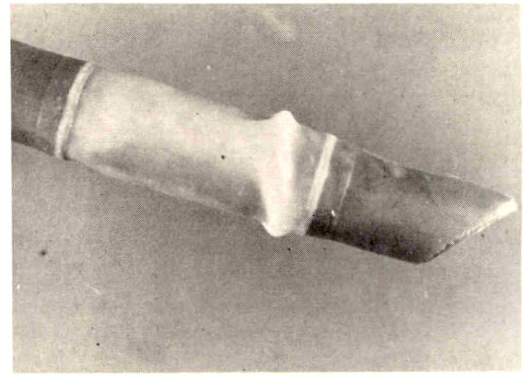


FIGURE. The collar-like ridge or "flange" formation at the distal end of the cuff of a red-rubber Murphy tube, preventing easy extubation.

DISCUSSION

Pavlin and associates[1] have described several cases of difficult removal of Portex Blue Line tracheostomy tubes, the cuffs of which have a large residual volume. Flange formation is more likely to occur in such cuffs than those with a small residual volume. Flange formation did not occur at room temperature nor with other makes of tracheostomy tubes with large residual volume cuffs incubated at 37° C for 30 minutes. The exact cause of the formation of these flanges is unclear.

Other important factors are: (1) the relation of tube and cuff size to the size of the tracheal stoma or laryngeal inlet; (2) lubrication of the tube and cuff prior to intubation, the lubricant being worn off during extubation; (3) the presence of stretching and

*Assistant Professor of Clinical Anesthesiology.
†Assistant Professor of Clinical Anesthesiology.
‡Department of Anesthesiology, University of Pittsburgh School of Medicine and Veterans Administration Hospital, Pittsburgh, Pennsylvania 15240.

Paper received: 2/6/76
Accepted for publication: 2/26/76

CLASSIFIED ADVERTISING

ANESTHESIOLOGY CHAIRMAN

The Hospital Center at Orange has an exceptional opportunity for a Board Certified or Board eligible Anesthesiologist with a minimum of 10 years experience to coordinate the activities of our Department of Anesthesiology as the Department Chairman. An affiliation with Medical School for a student and house officer training program is being pursued. The selected candidate will be considered for academic appointment to the New Jersey College of Medicine and Dentistry.

A competitive compensation package consisting of administrative fee or salary plus fee-for-service income will be available.

The Hospital Center has approximately 400 beds consisting of two units; namely The Orange Memorial Hospital and The New Jersey Orthopaedic Hospital Unit located in suburban N.J. offering convenient access to New York City and Philadelphia.

Send curriculum vitae to:
Arthur T. Dunn, President
THE HOSPITAL CENTER AT ORANGE
188 South Essex Ave.
Orange, New Jersey 07051
Equal Opportunity Employer

CHIEF OF ANESTHESIOLOGY

Major Midwestern medical center with a medical school affiliation is seeking an outstanding Anesthesiologist to head the Department of Anesthesiology. This is an immediate opportunity to restructure and/or build upon our current team. Our compensation package is exceedingly attractive and the working conditions are excellent as a result of our recently completed, multi-million-dollar expansion program. Please send curriculum vitae to: John D. Silbar, M.D., Chairman, Anesthesia Search Committee, Mount Sinai Medical Center, 950 North 12th Street, Milwaukee, Wisconsin 53233.

LOUISIANA—Tulane University, New Orleans. Immediate positions available for Academic Anesthesiologists in new Department of Anesthesiology. Positions in all anesthetic subspecialties, intensive care and respiratory therapy in new university teaching hospital. Tulane University is an Affirmative Action/Equal Opportunty employer. Curriculum vitae to: Robert R. Kirby, M.D., Department of Anesthesiology, Tulane University School of Medicine, 1430 Tulane Ave., New Orleans, Louisiana 70112.

PEDIATRIC ANESTHESIOLOGY RESIDENCY

Childrens Hospital of Los Angeles

Three-phase program: Clinical, Academic, Investigative, emphasizing practical aspects of anesthesiology related to infants and children.

AMA approval for third-year residency. Positions available from two months to one year.

Apply: George B. Lewis, Jr., M.D.
Head, Division of Anesthesiology
Childrens Hospital of Los Angeles
4650 Sunset Boulevard
Los Angeles, California 90054
Phone (213) 660-2450, Ext. 2262

DIRECTOR/SCHOOL OF NURSE ANESTHESIA. Immediate opening for CRNA with Masters Degree. We have a two-year program with university and medical school affiliation leading to a B.S. degree and CRNA certification. Ability to work independently in curriculum formation and school supervision is essential. Excellent salary and benefit package. If you are seeking a challenging position and career in a large medical teaching center, send resume with salary history and requirements to: Mrs. Anna Barker, Employment Manager, Medical Center Hospitals, Norfolk General Hospital Division, 600 Gresham Drive, Norfolk, Virginia 23507.

FACULTY POSITIONS

New University Department of Anesthesiology seeks full-time faculty (all levels) with interests in intensive care, ambulatory and obstetrical anesthesia. Also, full-time director of pediatric (not neonatal) intensive care and respiratory therapy. Challenging positions for those genuinely interested in teaching students and residents, research and development of a new Department. Pleasant university oriented community of 1,000,000. Excellent schools and living areas. Salaries negotiable. Send curriculum vitae to: R. Bryant Roberts, M.D., Professor and Chairman, Department of Anesthesiology, Wright State University School of Medicine, Dayton, Ohio 45431.

CHIEF ANESTHESIOLOGIST for 200-bed hospital—five modern OR's. All surgical services except open heart and neurosurgery. Excellent job challenge. Salary based on past experience and type of appointment. No malpractice insurance required. For information call or write to Dr. Zwemer, Chief Surgeon, Phoenix Indian Medical Center, 4212 North 16th Street, Phoenix, Arizona 85016. (602) 263-1200. The Indian Health Service is a Federal Employer and Federal Civil Service or Public Health Commissioned Corps benefits and requirements apply. Preference is given to qualified Indian or veteran applicants. IHS is an equal opportunity employer.

Classified Advertising (Continued)

ANESTHESIOLOGIST NEEDED—Board Certified desired with supervisory experience, now have three anesthesiologists and thirteen CRNAs doing all types surgery except open heart. Involved in intensive care, respiratory care, pain clinic, school for CRNAs and student and resident training cooperating with Jefferson Medical School. Lovely family community area. Call (412) 539-9711, ext. 273, or send resume to Mr. K. D. Bowman, Assistant Administrator, Latrobe Area Hospital, Latrobe, Pa. 15650. An equal opportunity employer.

CALIFORNIA—ANESTHESIOLOGISTS. Excellent opportunity to practice and participate in academically oriented program. Delightful California city. Favorable plan of remuneration and time off will be worked out. We can pay your professional liability insurance. Send curriculum vitae in first letter to: Jerome S. Harris, M.D., Director of Medical Affairs, Valley Medical Center, 445 S. Cedar, Fresno, California 93702.

ANESTHESIOLOGIST: Board certified/eligible to join newly formed group of anesthesiologists and nurse anesthetists in New Orleans. Fee for service private practice at 650-bed general hospital and newly opened Pediatric hospital. Write or call Metropolitan Anesthesia Associates, 4520 Melpomene, New Orleans, La. 70185. (504) 822-9331.

FACULTY POSITIONS

Department of Anesthesiology, Charity Hospital, New Orleans, affiliated with LSU and Tulane Medical Schools, has three faculty positions open for board certified/eligible anesthesiologists at Associate-Assistant Professor, Instructor levels. Duties involve teaching, research, clinical supervision. Salaries negotiable. Send inquiries and curriculum vitae to: M. Naraghi, M.D., Director, Department of Anesthesiology, Charity Hospital, New Orleans, Louisiana 70140.

MARYLAND: Positions on the Anesthesia Staff at Baltimore City Hospitals. Excellent fringe benefits and salary. Residency fully integrated with the Johns Hopkins Medical School program. Send CV to Peter Chodoff, M.D., Anes-in-Chief, Baltimore City Hospitals, 4940 Eastern Ave., Baltimore, Maryland 21224.

2 American anesthesiologists, eligible for oral boards in April 1977 from world-famous midwestern center, desire to relocate in Ohio or other state if center is attractive. Extensive experience in vascular, neuro and cardiovascular anesthesia. Contact Box 11-76-A in care of I.A.R.S.

ANESTHESIOLOGIST, 38, ABA certified, university trained, excellent references, seeks assoc. partner or group. No geographic preferences, prefer city or suburb. Available June 1977. Write to Box 11-76-B c/o I.A.R.S.

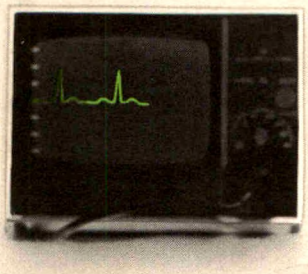
ANESTHESIOLOGIST—LOCUM TENEMS—1/77 - 3/77 in multispecialty center in NW lower Michigan. Excellent skiing and winter sports area. Michigan licensure necessary. Practice includes cardiac anesthesia and respiratory care. Share call with three other Board certified anesthesiologists. Contact: J. R. Rasmussen, M.D., c/o Burns Clinic Medical Center, P.C., 560 W. Mitchell, Petoskey, Michigan 49770.

ANESTHESIOLOGIST—BOARD CERTIFIED OR ELIGIBLE to assume position as director of and/or consultant to a hospital anesthesiology department in a new, rapidly growing, 171-bed Midwestern hospital; service area covers 150,000 residents and responds to a medical staff of 50-60 physicians; progressive city of 35,000 with excellent schools, cultural activities, and recreational oppotunities; salary $80,000 base and excellent compensation plan. •Send c.v. and references to Michael L. Wintory, Director of Personnel, St. Mary's Hospital, 3333 N. Seminary St., Galesburg, IL 61401.

Rates for classified advertising are $3.00 per line, minimum 5 lines. Box number ads $3.50 per line. Classified Display rates on request. Copy deadline 6 weeks prior to publication. Do not submit payment with order; invoices will be sent for payment prior to publication. Ad copy, subject to acceptance by publisher, should be mailed to: Anesthesia and Analgesia . . . Current Researches, 3645 Warrensville Center Rd., Cleveland, Ohio 44122.

IN PORTABLE ECG MONITORS...

CONVENTIONAL TRACES FADE FAST



AMERICAN OPTICAL'S DURA-VUE® DISPLAY GIVES YOU MORE TIME TO SEE THE ECG EVENT YOU DON'T WANT TO MISS

HOW VALUABLE CAN THAT BE UNDER BUSY O/R CONDITIONS?

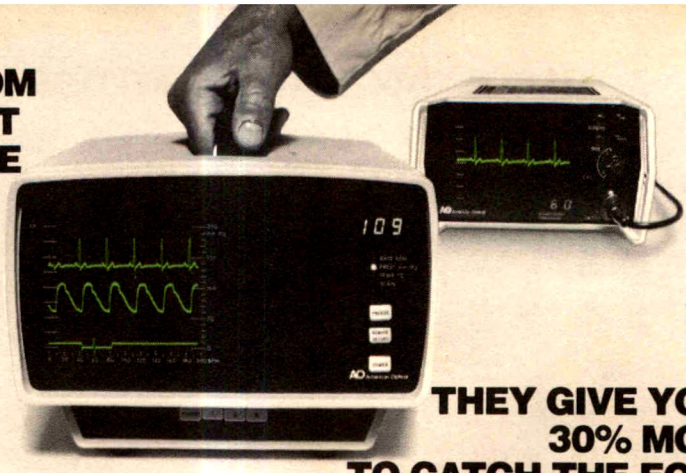
First Class
Permit No. 24
Bedford, MA

BUSINESS REPLY MAIL
No postage stamp necessary if mailed in the United States

Postage will be paid by:

American Optical MEDICAL DIVISION
Crosby Drive
Bedford, MA 01730

CHOOSE FROM 13 DIFFERENT AO PORTABLE MONITORS WITH DURA-VUE® DISPLAY



THEY GIVE YOU UP TO 30% MORE TIME TO CATCH THE ECG EVENT YOU DON'T WANT TO MISS

Line-Operated		Battery-Operated*
	ECG, Heart Rate, Systole Sound	1700
1600	ECG, Heart Rate, Alarms, Systole Sound	1601
1602	ECG, Digital Heart Rate, Alarms, Systole Sound	1603
1604	ECG, Digital Heart Rate, Alarms, Systole Sound, Blood Pressure/ Pulse	1605
1606	ECG, Alarms, Systole Sound, Digital Display with Scan of Heart Rate, Blood Pressure/Pulse, Temperature	1607
1608	Telemetry ECG, Heart Rate, Alarms, Systole Sound	1609
1610	Telemetry ECG, Digital Heart Rate, Alarms, Systole Sound	1611

*Battery-operated units can be operated from line while recharging except 1700.

AO®

American Optical MEDICAL DIVISION, Bedford, MA 01730

Gentlemen:

☐ Please have a salesman call for an appointment to explain more about the AO 1600 Series and 1700 Portable Monitors.

Name _____ Title _____

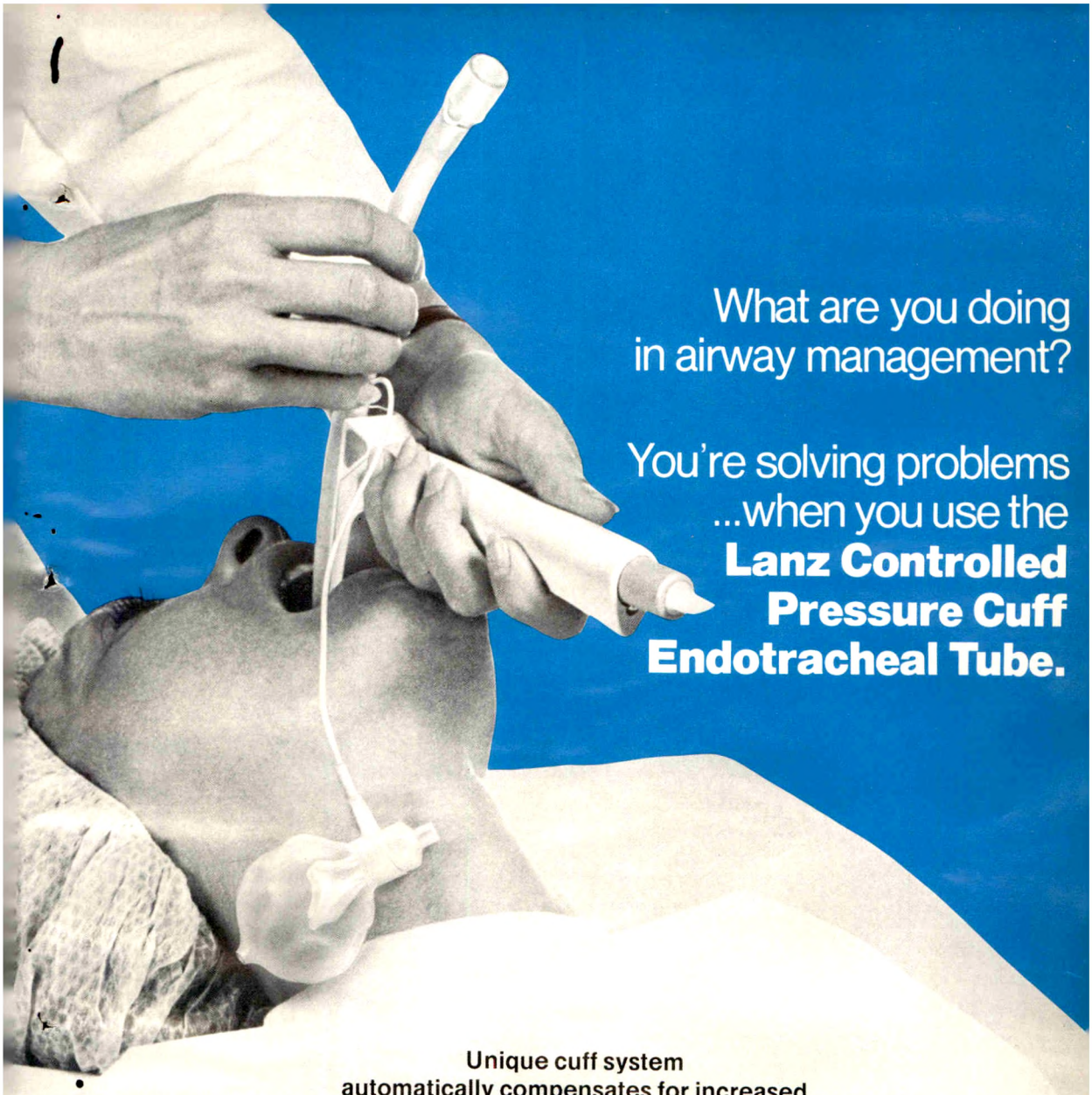
Hospital _____

Address _____

City _____ State _____ Zip _____

Telephone _____

© American Optical Corporation, 1976 7954 Printed in USA 7/76



What are you doing in airway management?

You're solving problems ...when you use the **Lanz Controlled Pressure Cuff Endotracheal Tube.**

Unique cuff system automatically compensates for increased volume/pressure caused by diffusion of N_2O or O_2 into cuff.

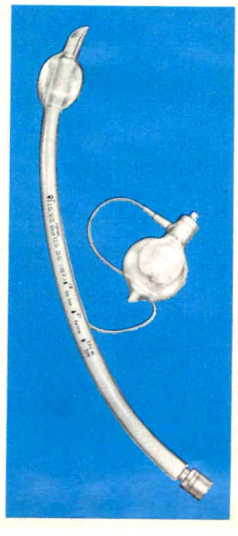
Long-term airway management is a problem. There's always the hazard of tracheal scarring and stenosis...accidental over-inflation. And so on.

Now with the Lanz Controlled-Pressure Cuff Endotracheal Tube, you can help solve your long-term intubation problems.

Dangers of Tracheal Damage Minimized.

The Lanz Endotracheal Tube is unique. It is a controlled-pressure cuff system containing an automatic, pressure regulating valve with an external, pressure-control balloon. This system is designed to eliminate excessive pressure on the tracheal wall due to over-inflation of the cuff. It's also designed to *automatically compensate* for increased volume and pressure caused by diffusion of N_2O or O_2 into the cuff.

When used in the intubation period before tracheostomy, it helps assure protection of the trachea throughout the entire period of airway management.



Patient Safety and Comfort

The Lanz Endotracheal Tube permits quick and easy intubation. The tube will flex, but not kink. It is available with either Murphy or Magill tips.

And it's available now—packaged sterile, and ready to use.

Help solve your long-term airway problems now with the Lanz Disposable Controlled-Pressure Cuff Endotracheal Tube. Write today for complete information, or call your Extracorporeal Representative.

extracorporeal

Extracorporeal Medical Specialties, Inc.
Royal & Ross Roads · King of Prussia Pa 19406 U.S.A. 215-337-2400

In Europe, write:
Extracorporeal S.A., 253 Avenue Winston Churchill, B-1180 Brussels, Belgium

Nesacaine®
(Chloroprocaine Hydrochloride)

1% and 2% solution in 30-ml. multiple-dose vials

For Infiltration and Regional Anesthesia

Nesacaine®-CE
(Chloroprocaine Hydrochloride)

2% and 3% solution in 30-ml. single-dose vials

For Caudal and Epidural Anesthesia

INDICATIONS

NESACAINE in multiple dose vials and NESACAINE-CE in single dose vials without preservatives are indicated for production of local anesthesia by infiltration injection and nerve block.*

*NESACAINE in multiple dose vials with preservatives is not to be used for caudal or epidural anesthesia. NESACAINE-CE contains no preservatives and the unused portion must be discarded after initial use.

CONTRAINDICATIONS

NESACAINE and NESACAINE-CE are contraindicated in patients hypersensitive to drugs of the PABA ester group. Central nervous system disease is generally considered a contraindication to caudal or epidural nerve block.

WARNINGS

RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE IMMEDIATELY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED. As NESACAINE-CE contains no preservative, discard unused drug remaining in vial after initial use. Equipment and drugs necessary for the treatment of inadvertent intravascular injection, intrathecal injection, or excessive dosage should be immediately available.

Usage in Pregnancy: Safe use of chloroprocaine hydrochloride has not been established with respect to adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential unless in the judgment of the physician the potential benefits outweigh the unknown hazards. In obstetrics, if vasoconstrictor drugs are used either to correct hypotension or are added to the local anesthetic solution, the obstetrician should be warned that some oxytocic drugs may cause severe persistent hypertension and even rupture of a cerebral blood vessel may occur during the post partum period.

Solutions containing vasoconstrictors, particularly epinephrine and norepinephrine, should be used with extreme caution in patients receiving certain antidepressants such as MAO inhibitors, and tricyclic compounds since a severe prolonged hypertension may occur.

PRECAUTIONS

The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious undesirable systemic side effects. Tolerance varies with the status of the patient. Debilitated patients, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical status.

Solutions containing vasoconstrictors should be used cautiously in the presence of disease which may adversely affect the patient's cardiovascular system.

Chloroprocaine hydrochloride should be employed cautiously in persons with known drug allergies or sensitivities.

The decision whether or not to use local anesthesia in the following conditions depends on the physician's appraisal of the advantages as opposed to the risk:

Paracervical block when fetal distress is anticipated or when predisposing factors causative of fetal distress are present (i.e., toxemia, prematurity, diabetes, etc.). Injection of solutions containing epinephrine in areas where the blood supply is limited (i.e., ears, nose, digits, etc.) or when peripheral vascular disease is present.

ADVERSE REACTIONS

Adverse reactions result from high plasma levels due to rapid absorption, inadvertent intravascular injection or excessive dosage. Hypersensitivity, idiosyncrasy, or diminished tolerance are other causes of reactions. Reactions due to overdosage (high plasma levels) are systemic and involve the central nervous system and the cardiovascular system.

Reactions involving the central nervous system are characterized by excitation and/or depression. Nervousness, dizziness, blurred vision or tremors may occur followed by drowsiness, convulsions, unconsciousness and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestations may be drowsiness merging into unconsciousness and respiratory arrest.

Reactions involving the cardiovascular system include depression of the myocardium, hypotension, bradycardia and even cardiac arrest.

Treatment of a patient with toxic manifestations consists of maintaining an airway, and supporting ventilation using oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system consists of using vasopressors, preferably those that stimulate the myocardium (e.g., ephedrine) and intravenous administration in small increments of an ultrashort acting barbiturate (i.e., thiopental, thiamylal) or a short acting barbiturate if these are not available (secobarbital, pentobarbital) or a short acting muscle relaxant (succinylcholine), together with oxygen. Muscle relaxants and intravenous barbiturates should be used only by those familiar with their use.

Allergic reactions are characterized by cutaneous lesions, urticaria, edema and other manifestations of allergy. The detection of sensitivity by skin testing is of doubtful value.

DOSAGE AND ADMINISTRATION

The maximum single recommended doses of chloroprocaine hydrochloride are: without epinephrine, 800 mg.; with epinephrine (1:200,000), 1000 mg. The recommended dosage is based on requirements for the average adult and should be reduced for elderly or debilitated patients and children.

The recommended doses given below serve only as a guide to the amount of anesthetic required for most routine procedures.

1. INFILTRATION AND NERVE BLOCK (NESACAINE)

Type of Block	Volume	Concentration
Occipital	3-5 ml.	1%-2%
Mandibular	2-3 ml.	2%
Maxillary	2-3 ml.	2%
Infra-orbital	0.5-1 ml.	2%
Cervical	3-4 ml. (for each segment)	1%-2%
Brachial plexus	30-40 ml.	2%
Ulnar nerve	3-5 ml.	2%
Paravertebral	3-5 ml.	2%
Intercostal	3 ml.	1%-2%
Sciatic nerve	10-15 ml.	2%
Stellate ganglion	5-10 ml.	1%-2%
Lumbar sympathetic (1 needle technic)	15-20 ml.	1%-2%
Interdigital	3-4 ml. (without epinephrine)	1%-2%

Fractional doses, up to 300 to 600 mg., may be given at 50 minute intervals.

2. CAUDAL AND EPIDURAL BLOCK (NESACAINE-CE)

For *caudal anesthesia* the initial dose is 15 to 25 ml. of a 2% or 3% solution. Repeated doses may be given at 40 to 60 minute intervals.

For *epidural anesthesia* in the lumbar and sacral regions 2.0 to 2.5 ml. per segment of a 2% or 3% solution can be used. The usual total volume of Nesacaine-CE is from 15 to 25 ml. Repeated doses 2 to 6 ml. less than the original dose may be given at 40 to 50 minute intervals.

HOW SUPPLIED

Nesacaine is supplied as follows:

1% solution (10 mg/ml.) in 30 ml. multiple-dose vials, 12 vials per carton.

2% solution (20 mg/ml.) in 30 ml. multiple-dose vials, 12 vials per carton.

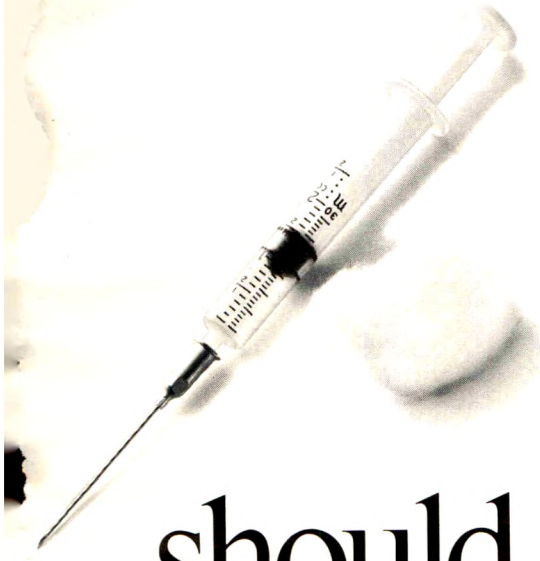
Nesacaine-CE is supplied as follows:

2% solution (20 mg/ml.) in 30 ml. single-dose vials, 12 vials per carton.

3% solution (30 mg/ml.) in 30 ml. single-dose vials, 12 vials per carton.

PENNWALT

Pennwalt Prescription Products
Pharmaceutical Division
Pennwalt Corporation
Rochester, New York 14603



A local anesthetic should meet your needs...

Rapid Onset of Action. Saves doctor, nurse and patient time.

Effective Anesthesia. Nesacaine (Chloroprocaine Hydrochloride) offers 80% to 90% pain-free procedures at recommended doses.

Exceptional Safety. Less potential for postoperative complications. Nesacaine is rapidly hydrolized in plasma, whereas lidocaine and other amide-type local anesthetics are metabolized in the liver. With Nesacaine, therefore, there is minimal potential risk of systemic toxicity, accumulation of metabolites, stimulation of CNS or cardiovascular effects.

Excellent Penetration. Chloroprocaine's lipid solubility and ionization characteristics impart it with excellent penetration.

Minimal Irritation at Injection Site. Few patient complaints about procedural pain, little soreness and inflammation after procedure.

Rapid and Complete Wear-Off. No residual numbness, patient back to normal faster.

See opposite page for brief prescribing information.

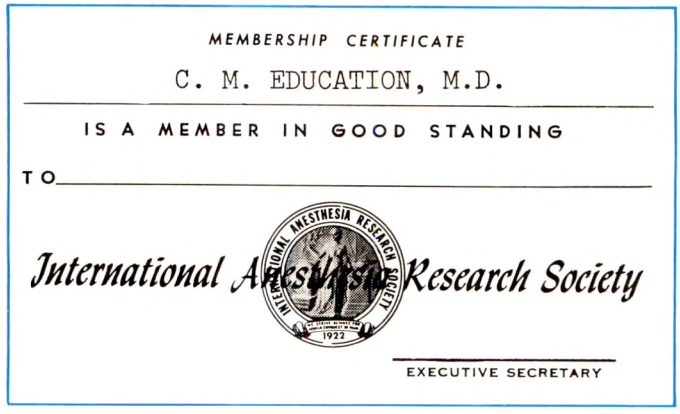
Look into

Nesacaine®

(Chloroprocaine Hydrochloride)

It meets your needs.

I. A. R. S. MEMBERSHIP
For Your In-training and Continuing Medical Education


MEMBERSHIP CERTIFICATE

C. M. EDUCATION, M.D.

IS A MEMBER IN GOOD STANDING

TO

International Anesthesia Research Society

EXECUTIVE SECRETARY

The International Anesthesia Research Society is a non-profit, scientific and educational corporation of the State of Ohio founded in 1922 "To Foster Progress and Research in Anesthesia." To this end it performs two functions: (1) It publishes a bi-monthly journal, "ANESTHESIA and ANALGESIA . . . Current Researches"; and (2) It sponsors an annual scientific "Congress" meeting which meets the criteria for Category 1 credit toward the AMA Physicians Recognition Award.

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state or national anesthesia organization.

MEMBERSHIP - ASSOCIATE MEMBERSHIP

MEMBERSHIP is open to individuals with doctorate degrees, licensed to practice in the medical, dental, osteopathic or veterinary medicine professions (i.e., MD, MB, DDS, DMD, DO, DMV); and to individuals with doctorate degrees (Ph.D.) in any scientific discipline, engaged in academic, private or commercial research.

ASSOCIATE MEMBERSHIP is open to individuals in the allied health professions, duly certified by their professional accrediting organization as nurse anesthetists (CRNA), physician assistants-anesthesia (PA-Anesth.), inhalation therapists (ARIT) or respiratory technicians (CRTT).

DUES are $25 per year for Members and Associate Members, and include a subscription to ANESTHESIA and ANALGESIA . . . Current Researches. Members are also entitled to reduced registration fee at IARS annual scientific meetings.

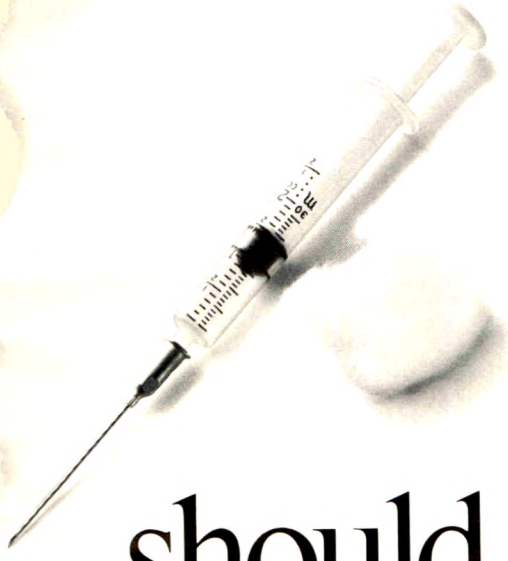
EDUCATIONAL MEMBERSHIP

EDUCATIONAL MEMBERSHIP is open to interns and residents in anesthesiology training programs; registered nurses enrolled in nurse anesthesia schools; students in inhalation or respiratory therapy training programs, or in physician assistant anesthesia programs.

The official Educational Membership application blank must be completed by the individual applicant, and signed by his or her training program director.

Dues are $25 for a single, two-year period during the member's anesthesia training period, and include a two-year subscription to ANESTHESIA and ANALGESIA . . . Current Researches. Educational Members are entitled to complimentary registration at IARS annual scientific meetings.

Application forms are available from Cleveland business office. Program Directors are invited to obtain a supply of Educational Membership applications for their students in training.



A local anesthetic should meet your needs...

Rapid Onset of Action. Saves doctor, nurse and patient time.

Effective Anesthesia. Nesacaine (Chloroprocaine Hydrochloride) offers 80% to 90% pain-free procedures at recommended doses.

Exceptional Safety. Less potential for postoperative complications. Nesacaine is rapidly hydrolized in plasma, whereas lidocaine and other amide-type local anesthetics are metabolized in the liver. With Nesacaine, therefore, there is minimal potential risk of systemic toxicity, accumulation of metabolites, stimulation of CNS or cardiovascular effects.

Excellent Penetration. Chloroprocaine's lipid solubility and ionization characteristics impart it with excellent penetration.

Minimal Irritation at Injection Site. Few patient complaints about procedural pain, little soreness and inflammation after procedure.

Rapid and Complete Wear-Off. No residual numbness, patient back to normal faster.

See opposite page for brief prescribing information.

Look into

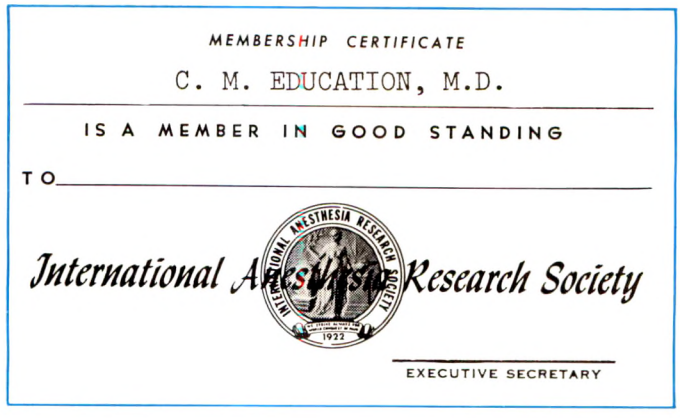
Nesacaine®

(Chloroprocaine Hydrochloride)

It meets your needs.

I. A. R. S. MEMBERSHIP

For Your In-training and Continuing Medical Education



The International Anesthesia Research Society is a non-profit, scientific and educational corporation of the State of Ohio founded in 1922 "To Foster Progress and Research in Anesthesia." To this end it performs two functions: (1) It publishes a bi-monthly journal, "ANESTHESIA and ANALGESIA . . . Current Researches"; and (2) It sponsors an annual scientific "Congress" meeting which meets the criteria for Category 1 credit toward the AMA Physicians Recognition Award.

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state or national anesthesia organization.

MEMBERSHIP - ASSOCIATE MEMBERSHIP

MEMBERSHIP is open to individuals with doctorate degrees, licensed to practice in the medical, dental, osteopathic or veterinary medicine professions (i.e., MD, MB, DDS, DMD, DO, DMV); and to individuals with doctorate degrees (Ph.D.) in any scientific discipline, engaged in academic, private or commercial research.

ASSOCIATE MEMBERSHIP is open to individuals in the allied health professions, duly certified by their professional accrediting organization as nurse anesthetists (CRNA), physician assistants-anesthesia (PA-Anesth.), inhalation therapists (ARIT) or respiratory technicians (CRTT).

DUES are $25 per year for Members and Associate Members, and include a subscription to ANESTHESIA and ANALGESIA . . . Current Researches. Members are also entitled to reduced registration fee at IARS annual scientific meetings.

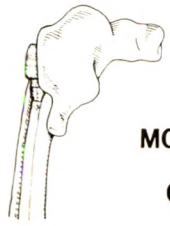
EDUCATIONAL MEMBERSHIP

EDUCATIONAL MEMBERSHIP is open to interns and residents in anesthesiology training programs; registered nurses enrolled in nurse anesthesia schools; students in inhalation or respiratory therapy training programs, or in physician assistant anesthesia programs.

The official Educational Membership application blank must be completed by the individual applicant, and signed by his or her training program director.

Dues are $25 for a single, two-year period during the member's anesthesia training period, and include a two-year subscription to ANESTHESIA and ANALGESIA . . . Current Researches. Educational Members are entitled to complimentary registration at IARS annual scientific meetings.

Application forms are available from Cleveland business office. Program Directors are invited to obtain a supply of Educational Membership applications for their students in training.



FOR MONOSCOPE MONITORING COMFORT CUSTOM EARPIECE

Made From Your Own Ear Impression

"Do It Yourself Impression Procedure" Proven At Many Hospitals Over Period of Several Years.

Impression Kit and Full Instructions Complete With Postage Prepaid Mailer $1.00

Lucite Custom Earmold With Coupler . . $8.50

One Week Delivery. Full Guarantee.
Full information upon request.

PLASTICAST LABORATORIES, INC.

711 Penn Ave. Pittsburgh, Pa. 15222

Telephone: (412) 281-3357

McGILL UNIVERSITY

ANNUAL REVIEW COURSE IN ANAESTHESIA—1977

May 23-27, 1977

This course is directed towards senior residents, candidates preparing for higher examinations and full time specialist anesthesiologists. The course content has been chosen to review important areas of scientific background and clinical practice, with emphasis on recent developments.

Teaching personnel consist of senior members of the McGill Faculty of Medicine together with a most distinguished guest faculty.

The meeting is held in a relaxed and attractive setting in McGill University.

FEE: $200.00
$100.00 (residents)

For further details write to:

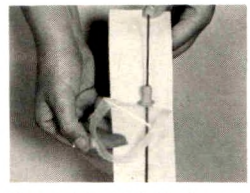
The Secretary
Post-Graduate Board
Royal Victoria Hospital
687 Pine Avenue, West,
Montreal H3A 1A1, Quebec

Update an old friend.

With the new universal SLICK™ STYLETTE endotracheal tube guide.

The old familiar way of intubating is not necessarily the better way. The better way to prepare for the unexpected during the critical period of induction and to increase the rate of successful first attempt intubations is to routinely use SLICK STYLETTE. Its non-friction coating eliminates the need for additional lubrication, and the stop-lock controls the extent of its advancement into the endotracheal tube. These features, plus its versatility and malleability reduce the difficulties encountered with normal anatomical variations, such as a small mouth, protruding teeth or bull neck as well as pathological obstacles.

Why not update your procedure with the addition of the SLICK STYLETTE as a standard part of your intubation pack—so it's always there when you need it?



Disposable Slick Stylette is packaged in a sterile Tyvek Mylar peel-away package. Fits all sizes and types of tubes from 3.5mm pediatric to 10.5mm adult.

Reg. U.S. Pat. Off.

Evaluation sample and literature on request.

Medical Products Div. P.O.L.A. Plastics Co., Dept. B
P.O. Box 2086, Van Nuys, Ca. 91408 (213)368-2002

Non-conductive blood pressure cuffs . . . in color!

Color-code your departments! Dupaco offers high quality non-conductive blood pressure cuffs in red, blue denim, paisley or plaid. Monogramming available up to 20 stitched letters, with department or individual's name.

Stain resistant, washable, with velcro attaching strips for Dupaco Diasyst.® Sizes listed below. For more information write: Dupaco Inc., P.O. Box 98, San Marcos, CA 92069.

Adult	5¾″ x 22″
Medium Adult	5″ x 17¾″
Child	3¾″ x 14½″
Infant	2¾″ x 11½″

DUPACO
INCORPORATED

FOR THE ATTENTION OF

PROGRAM DIRECTORS and STUDENTS IN MEDICAL, DENTAL, OSTEOPATHIC AND NURSE ANESTHESIA TRAINING PROGRAMS

Please clip and mail this to:

International Anesthesia Research Society
3645 Warrensville Center Rd., Cleveland, Ohio 44122

☐ I am a Program Director in an accredited anesthesia or anesthesia related (physician assistant, inhalation therapy) training program and would like to have _____ Educational Membership applications for students enrolled in my program.

☐ I am a student enrolled in an accredited anesthesia or anesthesia related training program. Please send me application for Educational Membership which includes a two-year subscription to ANESTHESIA and ANALGESIA . . . Current Researches for $25.

(NAME - PLEASE PRINT) (INSTITUTION)

(MAIL ADDRESS) (CITY, STATE AND ZIP)

INDEX OF ADVERTISERS

Air Products and Chemicals, Inc.—*Anesthesia Ventilator* ..... (42), (43)
Allergan Pharmaceuticals—*Lacri-Lube*® ..... (2)
American Optical, Medical Division—*Portable Monitors* ..... (61), (62)
Applied Medical Research—*Dinamap Monitor* ..... (27)
Ayerst Laboratories—*Fluothane*® ..... (6), (7), (8)
Burroughs Wellcome Company—*Anectine*® ..... (18), (19)
Concept, Inc.—*Pressurveil*(TM) ..... (25)
Datascope Corp.—*Monitors* ..... (21)
Dupaco Incorporated—*Liqui-Seal*(TM) *System* ..... (20)
Dupaco Incorporated—*Non-Conductive Blood Pressure Cuffs* ..... (68)
J. H. Emerson Company—*IMV Ventilator* ..... (10)
Endo Laboratories—*Narcan*® ..... (44), (45), (46)
Extracorporeal Medical Specialties, Inc.—*Lanz Endotracheal Tube* ..... (63)
Extracorporeal Medical Specialties, Inc.—*Swank*® *Transfusion Filter* ..... (26)
Fenwal Laboratories—*Operating Room System* ..... (49), (50), (51), (52)
Harris-Lake, Inc.—*Tec-Care Service Agreement* ..... (11), (12)
K & G Healthcare Industries, Inc.—*Nicholes "99" Filter* ..... (9)
McNeil Laboratories—*Sublimaze*® ..... (22), (23), (24)
Medical and Industrial Equipment Div., Claudius Ash, Inc.—
Jackson-Rees T-Piece ..... (47)
Medsonics, Inc.—*Versatone*® *Doppler* ..... (48)
Merck, Sharp & Dohme—*Aramine*® ..... (72)
North American Drager—*Narkomed Anesthesia Machine* ..... (33)
Ohio Medical Products—*Anesthesia System* ..... (14), (15)
O'Neal, Jones & Feldman, Inc.—*Antilirium* ..... (34)
Organon Inc.—*Pavulon*® ..... (29), (30), (31), (32)
Ped-Evac Company—*Ped-Evac*(TM) *Gas Evacuator* ..... (41)
Pennwalt Corporation—*Nesacaine*® ..... (64), (65)
Pharmaseal Laboratories—*Anesthesia Trays* ..... (70), (71)
Plasticast Laboratories, Inc.—*Custom Earmold* ..... (67)
P.O.L.A. Plastics—*Slick*(TM) *Stylette* ..... (67)
Professional Instruments Co.—*Peripheral Nerve Stimulator* ..... (28)
A. H. Robins Company—*Dopram*® ..... (16), (17)
Royal Victoria Hospital—*McGill University 1977 Review Course
in Anaesthesia* ..... (67)
Schuemann Labs. (Rals Laboratories Division)—*Rals Power Unit* ..... (41)
Winthrop Laboratories—*Marcaine*® ..... (56), (57), (58)

When to use the word Phär′mà·sēal.

For components, features, "performance" in single-use anesthesia trays, just say the word.

The trays you've counted on from the start now offer you even more to go on.

Back in 1963 we introduced the world's first single-use, regional anesthesia trays.

Today, with a record of safe performance difficult to equal, we offer you an even wider selection of components and features—just as difficult to match—in spinal, caudal and epidural trays.

All with our all-new spinal needle. The needle that's been called the cleanest spinal needle yet. The one with a cannula with almost uncanny smoothness, a cartridge pack with an exceptional point protector, a matched-ground point, metal hub and more.

Trays that offer you a new fenestrated drape with its own adhesive tabs.

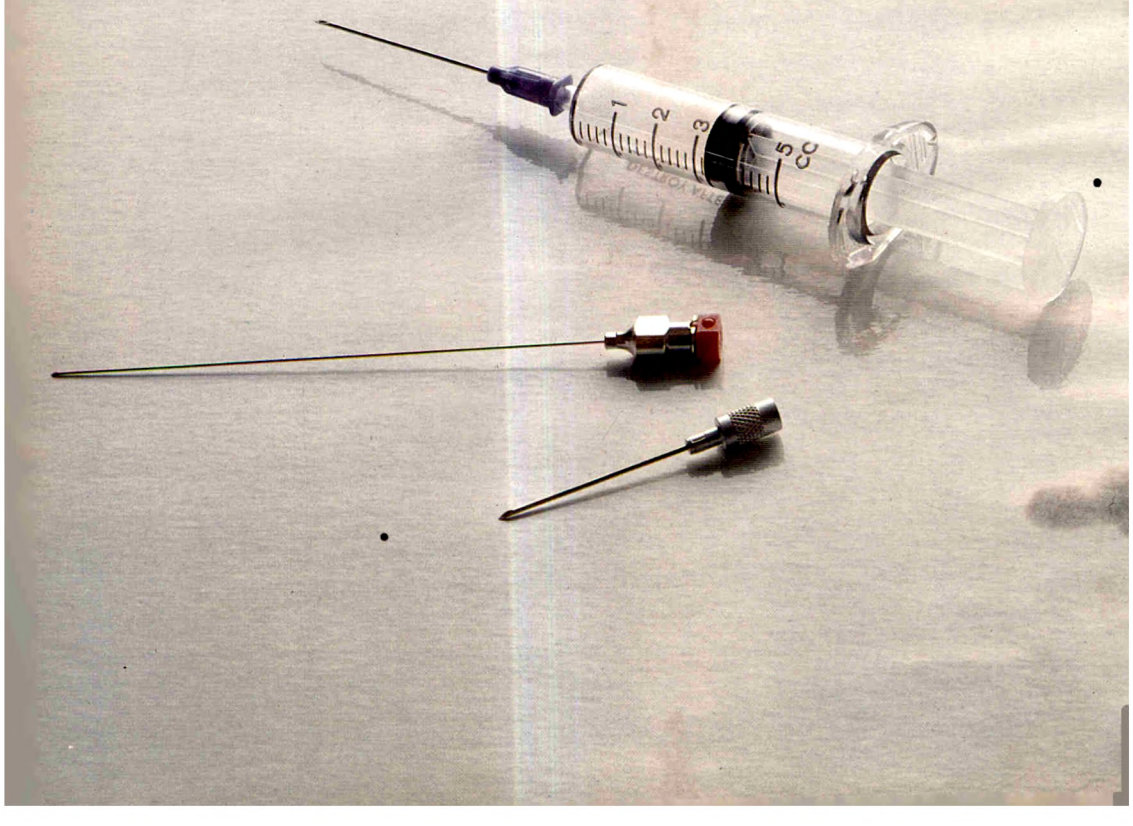
A large, moisture-resistant hospital wrap with a new "wrinkle for better procedure.

Plus, a specially designed introducer needle, a clear 5-cc. Stylex® syringe, a unique aseptic transfer carton...and a variety of other first-quality components and drugs.

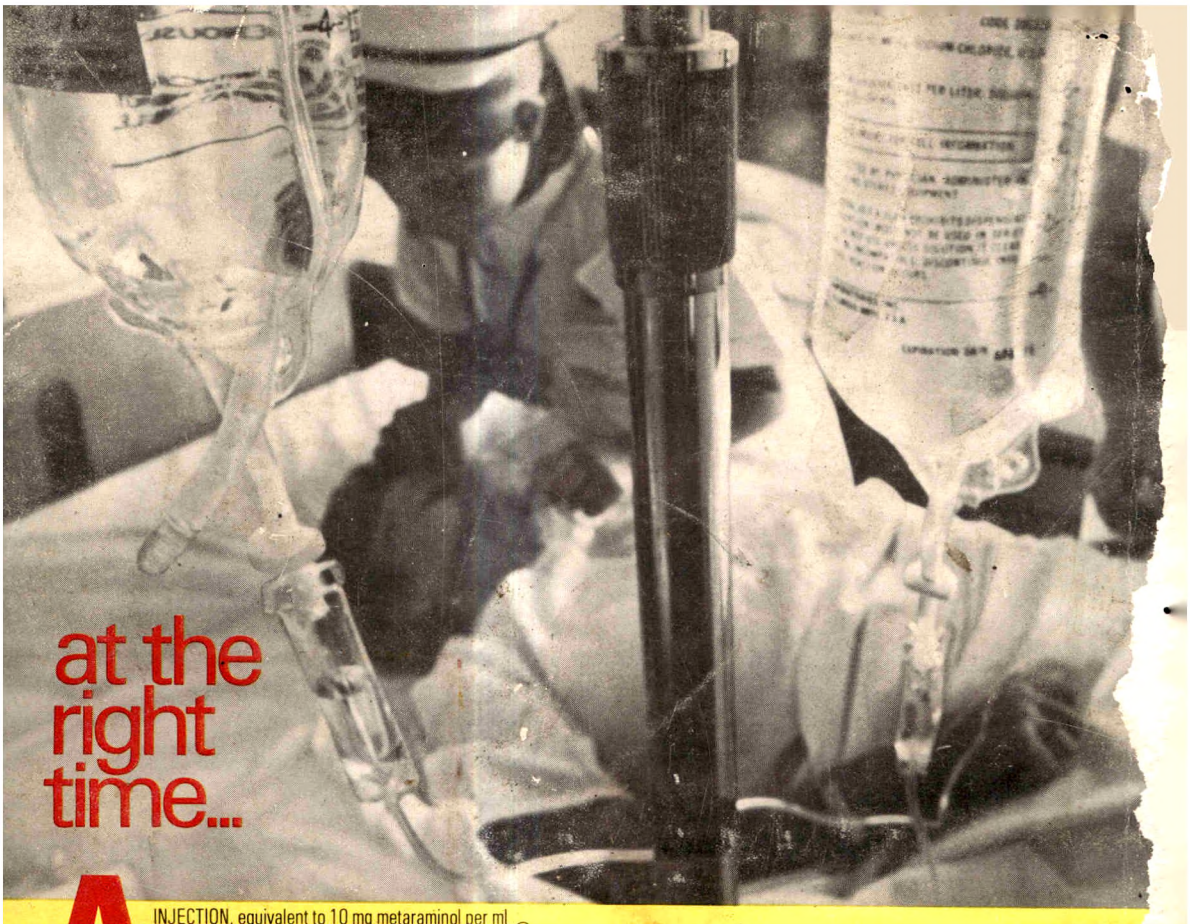
But see for yourself what we're talking about. See the trays with performance you can count on. For samples, just call or write.

You know the word to use.

O.R./ANESTHESIA PRODUCTS BY
PHARMASEAL
GLENDALE, CALIFORNIA 91201



SPINAL ANESTHES
with SPINAL ANEST
SPINAL NEEDLE, 25
LIDOCAINE
HYDROCHLORIDE
Injection, U.S.P.
1% w/v
3 ml
NDC 0252
DEXTROSE



at the right time...

INJECTION, equivalent to 10 mg metaraminol per ml

Aramine® (Metaraminol Bitartrate) MSD

a vasopressor with positive inotropic effect

Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:
Effective: ARAMINE is indicated for prevention and treatment of the acute hypotensive state occurring with spinal anesthesia. Adjunctive treatment of hypotension due to hemorrhage; reactions to medications; surgical complications; and shock associated with brain damage due to trauma or tumor.
"Probably" effective: It may also be useful as an adjunct in the treatment of hypotension due to cardiogenic shock or septicemia.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Use should be avoided with cyclopropane or halothane anesthesia, unless clinical circumstances demand such use.

Precautions: Use with caution to avoid excessive blood pressure response. Rapidly induced hypertensive responses have been reported to cause acute pulmonary edema, arrhythmias, and cardiac arrest. Use with caution in digitalized patients, since the combination of digitalis and sympathomimetic amines is capable of causing ectopic arrhythmic activity. Treat cirrhotic patients cautiously; if diuresis ensues, restore electrolytes. Fatal ventricular arrhythmia has been reported in one patient with Laennec's cirrhosis. In several instances, ventricular extrasystoles that appeared during infusion have subsided promptly on reduction of infusion rate. Since metaraminol has prolonged duration of action, a cumulative effect is possible, leading to prolonged elevation of blood pressure even with discontinuation of therapy. Monoamine oxidase inhibitors have been reported to potentiate action of sympathomimetic amines.
When vasopressor amines are used for long periods, resulting vasoconstriction may prevent adequate expansion of circulating volume and may cause perpetuation of the shock state. Plas volume may be reduced in all types of shock, and measurement central venous pressure is the most useful means of assessing t adequacy of the circulating blood volume; blood or plasma volur expanders should be employed for hypotension or shock due main to decreased circulating volume. Because of its vasoconstricto effect, metaraminol should be used with caution in heart or thyro disease, hypertension, or diabetes. Sympathomimetic amines m provoke relapse in patients with history of malaria.

Adverse Reactions: Sinus or ventricular tachycardia, or other rhythmias, especially in patients with myocardial infarct Abscess formation, tissue necrosis, or sloughing may rarely fo use. In choosing the site of injection, it is important to avoid th areas recognized as *not* suitable for use of any pressor agent, ar discontinue infusion immediately if infiltration or thrombosis curs. The larger veins of the antecubital fossa or the thigh are ferred to veins in the dorsum of the hand or ankle veins, particu in patients with peripheral vascular disease, diabetes mellit Buerger's disease, or conditions with coexistent hypercoagulabil

Note: Response to vasopressors may be poor in patients with co istent shock and acidosis. Established methods of shock man ment, such as blood or fluid replacement when indicated, and measures directed to the specific cause of the shock should be used. *Only Sodium Chloride Injection or 5 per Dextrose Injection should be used as a diluent.*

How Supplied: Injection, in 1-ml ampuls and 10-ml vials, cont ing per ml: metaraminol bitartrate equivalent to 10.0 metaraminol; inactive ingredients: sodium chloride, 4.4 mg for injection, q.s. ad 1.0 ml; and 0.15% methylparaben, 0.02 pylparaben, and 0.2% sodium bisulfite added as preservatives.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

M
M
S
D